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14. ABSTRACT

Recent research has shown the effectiveness of immunotherapy treatments in managing patients with both incurable and curable cancers. These immune checkpoint inhibitor treatments turn the patient's immune system against cancer cells, resulting in impressive and long-lived responses to cancer treatment in many patients. While incredibly effective for some, these treatments do not work for all patients and they are unfortunately associated with toxicities arising from the immune system attacking the patient's own body. So-called autoimmune toxicities can range from mild and self-limited, to severe and life threatening. The research reviewed here examines predictive features of these autoimmune toxicities. The goal is the development of a risk prediction model for autoimmune toxicities from cancer immunotherapy, with secondary goals examining the impact on survival from these immunotherapy induced autoimmune events and predictors of overall survival among cancer patients receiving immunotherapy.

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1. Introduction:

Immune checkpoint inhibitors (ICI) have revolutionized cancer therapy over the past decade. With extensive Federal Drug Administration (FDA) approvals in numerous cancer diagnoses, the impact of these therapies has been substantial. While effective and safe for some patients, the majority of those treated will not respond to ICI therapy, and therapy can be associated with substantial and life-changing autoimmune toxicities. The risk of treatment related autoimmune toxicities is currently described by clinical trials that were underpowered to detect their true incidence, and limited knowledge is known about relative risks of these toxicities among patients starting immunotherapy treatments. Additional knowledge of the risks of these autoimmune complications is needed, and validated tools to predict risks for an individual patient are crucial to ongoing counseling and treatment of individual patients. This grant's goal is to develop a risk prediction model for autoimmune toxicities related to ICI among cancer patients. Additional goals aim to better understand the impact of autoimmune toxicities on survival in cancer patients receiving ICI as well as better describe real-world rates of toxicities.

Objective: The objective of the proposed research is the development of a validated risk prediction tool for checkpoint inhibitor related autoimmune toxicities.

Specific Aims:

Aim 1 – To describe rates of autoimmune toxicities within a real-world patient dataset across multiple tumor types. We will utilize a large patient dataset from the VHA and WUSTL to describe observed rates of irAEs amongst patients receiving checkpoint inhibitors.

Aim 2 – To develop a risk prediction model for grade 3-4 immune related adverse events in patients receiving immunotherapy. We plan to utilize a large patient database from the VHA and WUSTL to develop a prediction model for immunotherapy toxicities.

Aim 3 – To assess the association between grade 3-4 immune related adverse events and clinical outcomes in patients receiving immunotherapy. We will conduct analyses of immune checkpoint inhibitor toxicity and its impact on PFS and OS amongst cancer patients treated with immune checkpoint inhibitors.

Study Design: This is a retrospective cohort study that is utilizing a large patient dataset of ICI recipients through the Veteran Affairs Health Administration and a second data set from Washington University in St. Louis. Rates of ICI toxicities are being assessed utilizing both datasets, and legacy as well as machine learning techniques will be utilized to determine the optimal risk prediction model for the development of autoimmune toxicities.

Impact: The research proposed is innovative and important for several reasons. (1) It will provide vital information about rates of ICI toxicities in a racially and economically diverse population. (2) It will develop and validate a crucial risk prediction tool that will help inform patients and physicians as to the relative risks of ICI related autoimmune toxicities. (3) It will investigate the relationships between toxicities and outcomes amongst ICI recipients, an evolving area of research. These findings will directly inform and impact patient care in an immediate manner, improving the management and outcomes of many cancer patients

2. Keywords

Immunotherapy, Cancer, Autoimmune, Immune related adverse events, Checkpoint inhibitors, Oncology, Immunology, Outcomes Research, Machine Learning, Regression analysis.

3. Accomplishments

We have had ongoing accomplishments on the research project and several ongoing difficulties/obstacles. Interesting findings on the impact of time of therapy administration have opened up new areas of interest in the research endeavor. We will review status of the ongoing project and next steps as outlined below.

MAJOR TASK 1: *Regulatory Approval and Credentialing*

Task Overview: All necessary regulatory approvals have been obtained. Annual reviews have proceeded without issues.

- ***Subtask 1: IRB Approvals at WUSTL and STLVAMC***
    - This has been completed prior, all approvals obtained/established by August 2020
- ***Subtask 2: VA WoC Appointments for WUSTL collaborators***
    - This has been completed for key investigators, and for a collaborating team of chart abstractors (Washington University Resident Physicians). However, some team members have not necessitated a without compensation appointment at the St. Louis VA Medical Center (Inez Oh, PhD and Randi Foraker, PhD).
- ***Subtask 3: Data sharing arrangements for WUSTL and STLVAMC***
    - The sharing of data at this time in the grant is not necessary and we have pushed forward with alternate aims of the grant. Potential workarounds for this component of the grant have been developed (model sharing instead of data sharing).
- ***Subtask 4: Coordinate with sites for annual IRB approval, continuing review annually***
    - Subsequent annual reviews have been approved at the St. Louis VA Medical Center.
    - Washington University in St. Louis subsequent annual review is approved.
- ***Subtask 5: HRPO review/approval of IRB protocols***
    - HRPO approval reviews completed at all sites and DOD.

MAJOR TASK 2: *Analysis of VA and WUSTL data to obtain rates of autoimmune toxicities*.

Task Overview: The analysis of the dual datasets at the St. Louis Veterans Affairs Medical Center and Washington University is ongoing. Several key tasks have already been completed. The initial plan to utilize ICD Codes to identify toxicities has been employed with success, however a recent publication has raised potential complications to this approach. In an article entitled *Comparative assessment of manual chart review and ICD claims data in evaluating immunotherapy-related adverse events* by *Nashed, Zhang, et al*, a curated list of ICD codes was found to be ineffective at capturing autoimmune toxicity events among cancer patients receiving immunotherapy. As such, the abstraction of charts has become a significantly more important component of the study. This will add additional time, and has delayed some components of the tasks below. **At the present time we have been successful at identifying Prednisone prescription as a highly sensitive and reasonably specific mechanism of identifying autoimmune toxicities among patients with Melanoma. We plan to continue this approach of abstraction through Lung (ongoing), Genitourinary malignancies and Head and Neck Squamous Cell Carcinoma.**

Subtask 1: Identify ICD9/10 codes for autoimmune toxicities of interest

- Based off a study through Ohio State University and our own analysis, we have identified a comprehensive list of candidate ICD codes for autoimmune toxicities of interest. Key autoimmune toxicities that would routinely result in alteration of therapy and administration of steroid therapy were chosen. Broadly these fall into three main groups, including Pulmonary, Hepatic and GI (colitis) events. These are all listed below via table form, in significant detail, within Table 1, 2 and 3:

Table 1: Pneumonitis/Pulmonary Autoimmune ICD Toxicity Codes

Pneumonitis Diagnosis	ICD10	ICD9	Pneumonitis Diagnosis	ICD10	ICD9	Pneumonitis Diagnosis	ICD10	ICD9
Drug induced pneumonitis	J70.4	508.8	Dyspnea	R06.2	786.07	Chronic respiratory failure, with hypercapnia	J96.12	518.8
Acute drug-induced interstitial lung disorders	J70.2	508.8	Chest pain on breathing	R07.1	786.52	Acute and chronic respiratory failure, unspecified whether with hypoxia or hypercapnia	J96.20	518.5
Pneumonitis due to inhalation of other solids and liquids	J69.8	507.8	Acute respiratory failure, unspecified whether with hypoxia or hypercapnia	J96.00	518.51	Acute and chronic respiratory failure, unspecified whether with hypoxia or hypercapnia	J96.20	518.8
Cough	R05	786.2	Acute respiratory failure, unspecified whether with hypoxia or hypercapnia	J96.00	518.81	Acute and chronic respiratory failure, with hypoxia	J96.21	518.5
Dyspnea, unspecified	R06.00	786.1	Acute respiratory failure, with hypoxia	J96.01	518.51	Acute and chronic respiratory failure, with hypoxia	J96.21	518.8
Orthopnea	R06.01	786	Acute respiratory failure, with hypoxia	J96.01	518.81	Acute and chronic respiratory failure, with hypercapnia	J96.22	518.5
Shortness of breath	R06.02	786.1	Acute respiratory failure, with hypercapnia	J96.02	518.51	Acute and chronic respiratory failure, with hypercapnia	J96.22	518.8
Acute respiratory distress	R06.03	518.8	Acute respiratory failure, with hypercapnia	J96.02	518.81	Respiratory failure, unspecified, unspecified whether with hypoxia or hypercapnia	J96.90	518.8
Acute respiratory distress	R06.03	770.9	Chronic respiratory failure, unspecified whether with hypoxia or hypercapnia	J96.10	518.83	Respiratory failure, unspecified, with hypoxia	J96.91	518.8
Other forms of dyspnea	R06.09	786.1	Chronic respiratory failure, with hypoxia	J96.11	518.83	Respiratory failure, unspecified, with hypercapnia	J96.92	518.8

Table 2: Hepatic Autoimmune ICD Toxicity Codes

Hepatitis Realated Diagnosis	ICD10	ICD9	Hepatitis Related Diagnosis	ICD10	ICD9
Autoimmune hepatitis	K75.4	571.42	Hepatic sclerosis	K74.1	571.9
Nonspecific reactive hepatitis	K75.2	573.3	Hepatic fibrosis with hepatic sclerosis	K74.2	571.9
Other chronic hepatitis, not elsewhere classified	K73.8	571.49	Primary biliary cirrhosis	K74.3	571.6
Hepatic failure, unspecified with coma	K72.91	572.2	Secondary biliary cirrhosis	K74.4	571.6
Hepatic failure, unspecified with coma	K72.91	572.8	Biliary cirrhosis, unspecified	K74.5	571.6
Hepatic failure, unspecified without coma	K72.90	572.8	Unspecified cirrhosis of liver	K74.60	571.5
Acute and subacute hepatic failure without coma	K72.00	570	Other cirrhosis of liver	K74.69	571.5
Acute and subacute hepatic failure with coma	K72.01	570	Toxic liver disease with hepatic necrosis, without coma	K71.10	573.3
Acute and subacute hepatic failure with coma	K72.01	572.2	Toxic liver disease with hepatic necrosis, with coma	K71.11	572.2
Inflammatory liver disease, unspecified	K75.9	573.3	Toxic liver disease with hepatic necrosis, with coma	K71.11	573.3
Toxic liver disease with acute hepatitis	K71.2	573.3	Nonspecific elevation of levels of transaminase and lactic acid dehydrogenase	R74.0	790.4
Liver disorders in diseases classified elsewhere	K77	573.8	Obstruction of bile duct	K83.1	576.2
Hepatic fibrosis	K74.0	571.5	Disorder of bilirubin metabolism, unspecified	E80.7	277.4

Table 3: GI Autoimmune ICD Toxicity Codes

Colitis	ICD10	ICD9	Colitis	ICD10	ICD9
Toxic gastroenteritis and colitis	K52.1	558.2	Eosinophilic gastritis or gastroenteritis	K52.81	535.71
Other specified noninfective gastroenteritis and colitis	K52.89	558.9	Eosinophilic gastritis or gastroenteritis	K52.81	558.41
Other specified noninfective gastroenteritis and colitis	K52.89	787.91	Eosinophilic colitis	K52.82	558.42
Indeterminate colitis	K52.3	558.9	Collagenous colitis	K52.831	558.9
Gastroenteritis and colitis due to radiation	K52.0	558.1	Lymphocytic colitis	K52.832	558.9
Toxic gastroenteritis and colitis	K52.1	558.2	Other microscopic colitis	K52.838	558.9
Food protein-induced enterocolitis syndrome	K52.21	558.3	Microscopic colitis, unspecified	K52.839	558.9
Food protein-induced enteropathy	K52.22	558.3	Noninfective gastroenteritis and colitis, unspecified	K52.9	558.9
Other allergic and dietetic gastroenteritis and colitis	K52.29	558.3	Diarrhea	R19.7	787.91
Other allergic and dietetic gastroenteritis and colitis	K52.29	787.91	Unspecified abdominal pain	R10.9	789
Eosinophilic gastritis or gastroenteritis	K52.81	535.7	Melena, blood in stool	K92.1	578.1
Mucus in stool	R19.5	787.7			

Subtask 2: Evaluate pharmacy data to identify patients receiving steroids

- We have identified within both our Veterans Affairs Dataset and the Washington University in St. Louis dataset those patients receiving an outpatient prescription of Prednisone (steroid-therapy) following an initial dose of a checkpoint inhibitor up to 6 months after their final dose of a checkpoint inhibitor. These numbers and details are presented below:

Table 4: Checkpoint inhibitor administered and Number of patients receiving prednisone in Washington University Dataset

Medication Administered	Number of Patients	Patients Receiving Prednisone
Pembrolizumab	695	82
Nivolumab	1078	157
Ipilimumab	333	79
Totals:	2106	318

Table 5: Patient Diagnosis, Drug Therapy and Toxicity Identification by ICD Code and Prednisone Prescription from VA

Diagnosis	Number of Patients	Toxicity by ICD Code	Toxicity By Prednisone Prescription
Esophageal Cancer	65	17	14
Trachea/Bronchus/Lung	1991	499	510
Stomach/Gastric	30	13	4
Head and Neck Cancer	364	97	58
Colon Cancer/Rectal CA	79	26	15
Liver Cancer	219	70	41
Bladder Cancer	364	136	75
Kidney Cancer	286	87	80
Melanoma	399	106	99
Breast Cancer	0	0	0
Neuroendocrine	46	10	5
Hodgkin Lymphoma	8	4	4
Immunotherapy Drugs			
Pembrolizumab	2140	418	434
Ipilimumab	265	59	79
Atezolizumab	396	65	79
Nivolumab	1867	464	419
Durvalumab	335	49	91
Cemiplimab	18	2	3
Avelumab	3	0	0

Table 6: Patient Diagnosis, Toxicity Identification by ICD Code from VA

VA RESULTS: ICD Codes to ID Toxicities By Disease of Diagnosis

Diagnosis	Number of Patients	Colitis	Regional Enteritis	Hepatitis	Renal Toxicity	Pneumonitis
Esophageal Cancer	65	9	0	0	8	7
Trachea/Bronchus/Lung	1991	190	2	25	253	155
Stomach/Gastric	30	6	0	1	1	3
Head and Neck Cancer	364	37	0	2	48	38
Colon Cancer/Rectal CA	79	14	1	1	15	4
Liver Cancer	219	26	0	8	44	7
Bladder Cancer	364	42	1	6	101	22
Kidney Cancer	286	35	3	7	56	13
Melanoma	399	45	2	5	55	14
Breast Cancer	0	0	0	0	0	0
Neuroendocrine	46	6	0	0	8	1
Hodgkin Lymphoma	8	1	0	0	3	1
Total:	3851					

Table 7: Patient Diagnosis, Toxicity Identification by ICD Code from Washington University

Cancer Type	Number of Patients Receving Prednisone
Neuroendocrine	9
Lung	91
Esophageal	8
Stomach	5
Head and Neck	33
Kidney	21
Liver	11
Melanoma	72
Colorectal	19
Hodgkin Lymphoma	9
Breast	19
Bladder	6

These results are outlined in Tables 4, 5, 6 and 7. Table 4 provides a brief overview of varieties of checkpoint inhibitor administered and the numbers of patients within each group receiving prednisone (potential autoimmune toxicities) within the Washington University dataset. Table 5 outlines patient diagnosis, drug treatment and toxicity identification with ICD codes and Prednisone prescription from the VA. Table 6 outlines (using VA data) the indicence of particular toxicities by disease state. Table 7 shows the close correlation of ICD code toxicities with Prednisone prescriptions from Washington University.

Given the unreliable correlation of ICD codes with the occurrence of real irAEs, we have aimed to confirm that the outpatient prescription of a certain dose of Prednisone is correlated with a real autoimmune toxicity. We have, over the last calendar year, completed the abstraction of patients from the Melanoma cohort (356 patients). Direct abstraction was extremely time-consuming and has taken longer than anticipated. Overall, we found that Prednisone prescription is a very reliable mechanism of identification of immune related autoimmune toxicities and is associated with a 100% sensitivity and a 76% specificity for the detection of autoimmune events in our Melanoma cohort. The gross numbers are outlined below in Table 8 and test characteristics are seen in Table 9. Removing patients with steroids prescribed for brain metastases resulted in a much improved specificity (88%) and PPV (0.79). This is outlined in Table 9 and 10 below. This finding provides an approach to identify cases of irAEs administratively. We are in the process of writing up and publishing this finding. Furthermore, we hope to apply this to portions of the cohort that may be difficult to finish abstracting given time remaining on the grant and personnel issues.

Table 8: Prednisone Prescription for Identification of irAE: Gross Numbers from Abstracted VA Cohort

Prednisone And irAEs	Positive for irAE	Negative for irAE	Total
Positive Prednisone Prescription	97	63	160
Negative Prednisone Prescription	0	196	196
Totals	97	259	

Table 9: Prednisone Prescription for Identification of irAEs: Test Characteristics

True Positives	97
True Negatives	196
False Positive	63
False Negatives	0
Sensitivity	1
Specificity	0.757
PPV	0.61
NPV	1

Table 10: Prednisone Prescription for Identification of irAE: Steroids for Brain Metastases Removed

Prednisone And irAEs	Positive for irAE	Negative for irAE	Total
Positive Prednisone Prescription	97	26	123
Negative Prednisone Prescription	0	196	196
Totals	97	222	

Table 11: Prednisone Prescription for Identification of irAE: Steroids for Brain Metastases Removed

True Positives	97
True Negatives	196
False Positive	26
False Negatives	0
Sensitivity	1
Specificity	0.88
PPV	0.79
NPV	1

Subtask 3: Comparison of patients identified in ST1 with ST2 4-7

- We have performed initial analyses within the Veterans Affairs population of the clinical/demographic characteristics of patients who have received prednisone versus those that have not. Initial analyses of patient characteristics, including rates of comorbidities, sex, age, and tumor type are described below in Table 12. Additional assessments including rates of toxicities by immunotherapy received are outlined in the Table above.

Table 12: Patient Diagnosis, Toxicity Identification by ICD Code from VA

Demographic clinical characteristics	Total (N=2,841)		P-value
	Prednisone Yes n=361	Prednisone No n=2,480	
Age (mean years, range)	68.7 (71)	68.7 (68)	0.20†
Male (%)	95.6	96.9	0.19*
Charlson score index (mean)	4.6	4.5	0.68†
Cancer type (%)			0.02*
Bladder	6.4	8.1	
Colon/Rectal	0.8	1.1	
Esophageal	1.7	1.2	
Head and Neck	3.6	8.5	
Hodgkin Lymphoma	0.6	0.2	
Kidney	9.4	5.9	
Liver	5.5	5.4	
Melanoma	12.7	11.5	
Neuroendocrin	0.6	0.7	
Stomach	0.3	0.7	
Trachea/Bronchus/Lung	58.5	56.9	
* Chi-square test			
† T-test			

- ***Subtask 4: Abstraction of charts to confirm toxicities found in ST1&ST2***
  - **Abstraction has continued to be very time consuming. We have additionally had some difficulties with abstraction staff turnover. As noted in prior year reports, the onboarding of an abstractor team has been somewhat hampered by excess clinical responsibilities during the COVID-19 pandemic as residents had less free time than anticipated during the planning and design stages of the project. Additionally there has been attrition in the abstractor team members. We are working to improve this. Accomplishments to date include:**
    - **Complete abstraction of Melanoma sub-cohort**
    - **Complete abstraction of Durvalumab (a checkpoint inhibitor) sub-cohort**
    - **Ongoing abstraction of Lung, Head and Neck and GU cohorts (Bladder/Renal)**
  - **At this time, we have achieved additional funding from Washington University in St. Louis via Resident research grants (Mentors in Medicine) for two additional abstractors, and have one additional Medical Student involved. We are challenged by abstraction, but have**

adopted additional strategies to overcome this issue (use of Prednisone prescription as a marker for irAEs), and have additional options should this continue to be a roadblock to progress.

- ***Subtask 5: Compilation of data and reporting of findings***
    - **This is still ongoing and we are awaiting abstraction results prior to compilation/publication as this will make our findings and conclusions more definitive.**
- ***Subtask 6: Manuscript preparation and publication***
    - **As above, this is still ongoing due to progress on abstraction of charts and adjudication of immunotherapy toxicity events. However, several posters and publications have already been produced and are included at the end of the report.**

MAJOR TASK 3: *To develop a classic regression based risk prediction model*

Task Overview: We have proceeded with the development of a risk prediction model to predict both the development of autoimmune toxicities (model 1) and overall survival (model 2) for cancer patients receiving immunotherapy. We have utilized prednisone prescription to identify patients experiencing autoimmune toxicities (method still pending validation) and have reliable markers of survival based from VA death records. Results are detailed below. Final risk model development is still in progress at this time, but univariate and initial multivariate analyses have been completed. **Additional Machine Learning models have been utilized over the past year to help establish predictors of OS and autoimmune toxicities and these are presented below in the appropriate sections.**

- ***Subtask 1: Classification of patients with autoimmune toxicity as in Aim 1***
    - As detailed above patients who have developed a presumed autoimmune toxicity event have been identified within the dual datasets at the St. Louis VA and Washington University via two methods: ICD codes and Prednisone prescription. These determinations (outlined above) have been utilized to identify toxicity events.

- ***Subtask 2: Establishment of candidate predictors and covariates for model***

We have examined various candidate predictors for potential autoimmune events as well as overall survival for patients undergoing checkpoint inhibitor therapy for a cancer diagnosis. The key components of the current analyses are included in Table 13. Additional planned assessments include leukocyte subsets (absolute neutrophil count, absolute lymphocyte count and absolute eosinophil count), concurrent medications (statin therapy, hypoglycemic therapy), prior antibiotic history, impact of racial disparities, and geographic details. A particularly detailed sub-analysis of metabolic impacts of autoimmune toxicities and overall survival among those receiving immunotherapy will be pursued. The role of these factors have been established through extensive review of the literature as well as analyses of our own data sources. Many of these analyses have been completed, but some are actively ongoing and details of these will be presented below.

Table 13: Univariate Predictors Examined for Survival/Toxicity

Univariate Predictors Examined
Age
Cancer Diagnosis
Immunotherapy Drug Received
Charlson Comorbidity Index
History of Dementia
History of Stroke
History of Peptic Ulcer Disease
History of Connective Tissue Disease
History of Myocardial Infarction
History of Hemiplegia
History of Leukemia or Lymphoma
History of Diabetes Mellitus
History of Heart Failure
History of Peripheral Vascular Disease
History of Renal Disease
History of HIV Infection
History of Liver Disease
Albumin Levels
Creatinine
White Blood Cell Count
Hemoglobin
Body Mass Index

- ***Subtask 3: Univariate analysis of candidate predictors in VA dataset***
    - We have performed initial univariate analyses of candidate predictor variables for patients within the Veterans Affairs dataset. Outcomes assessed included associations with prednisone prescription and association with overall survival at 1 and 2 years. An extensive list of candidate predictors was considered as outlined in Table 13. Candidate predictors that were found to have a significant univariate association are presented in Tables 14, 15 and 16. Associations were examined between potential predictors and prednisone prescription (marker of autoimmune toxicity) as well as overall survival at 1 and 2 years.

Table 14: Univariate Association with Prednisone Prescription

Univariate Associarteion with Prednisone Prescription

Variable	OR	95% CI	P-value
Kidney	1.404	0.968, 2.039	0.07
Bladder	0.657	0.431, 1.001	0.051
Lung	1.296	1.056, 1.589	0.01
Pembrolizumab	0.821	0.669, 1.007	0.06
Atezolizumab	0.627	0.394, 0.999	0.049
Durvalumab	1.874	1.344, 2.613	0.0002
CPD	1.365	1.100, 1.695	0.005
albumin<3	0.451	0.342, 0.596	<0.0001
1<=creatinine <1.5	1.24	1.002, 1.536	0.045
10<=HgB<=13	0.77	0.618, 0.959	0.03
Hgb<10	0.366	0.267, 0.502	<0.0001
BMI <18.5	0.572	0.359, 0.911	0.0004
30<BMI<=35	1.699	1.268, 2.277	0.0003

Table 15: Univariate Association with Overall Survival at 1 Year

Univariate Analysis for Overall Survival at 1 Year

Variables	HR	95% CI	P-Value
Age	1.01	1.002, 1.020	0.02
Atezolizumab	1.38	1.15, 1.67	0.001
Durvalumab	0.28	0.21, 0.40	<0.0001
Charlson Score index	1.02	1.01, 1.04	0.004
HF	1.27	1.13, 1.43	<0.0001
CVD	1.15	1.02, 1.29	0.03
Hepatic Disease	1.39	1.09, 1.77	0.01
Liver disease	1.2	1.07, 1.34	0.002
BMI (2841)			<0.0001
BMI <18.5	1.83	1.56, 2.14	
18.5<=BMI<25 (ref)			
25<=BMI<30	0.63	0.56, 0.72	
BMI>=30	0.51	0.43, 0.59	

Table 16: Univariate Association with Overall Survival at 2

Univariate Association with Overall Survival at 2 Years

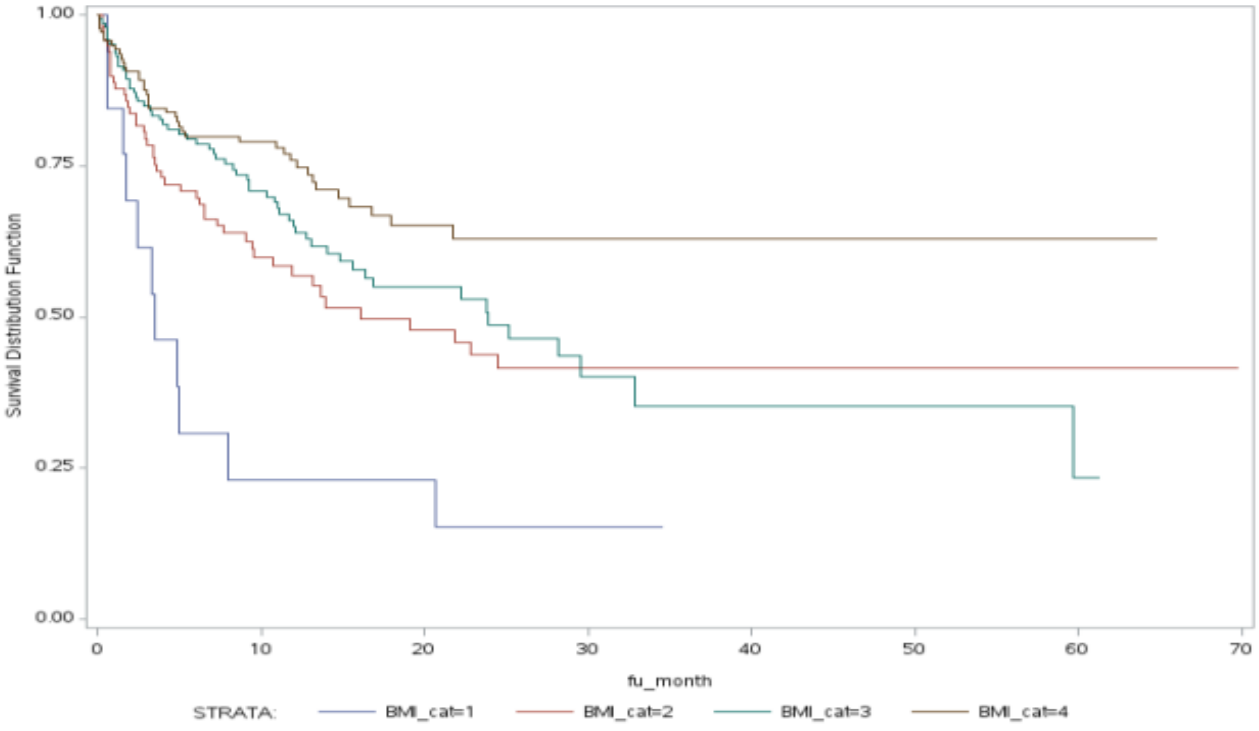
Variables	HR	95% CI	P-Value
Esophageal	2.24	1.57, 3.20	<0.0001
Bladder	1.29	1.10, 1.52	0.002
Liver	1.36	1.12, 1.65	0.002
Melanoma	0.54	0.46, 0.65	<0.0001
Durvalumab	0.33	0.25, 0.43	<0.0001
Charlson Score index	1.02	1.01, 1.04	0.003
HF	1.27	1.14, 1.42	<0.0001
PVD	1.11	1.01, 1.23	0.03
CVD	1.13	1.02, 1.26	0.03
Hepa	1.31	1.05, 1.65	0.02
Liver disease	1.15	1.04, 1.28	0.01
3<=albumin<=3.5	2.28	2.02, 2.58	
albumin<3	6.48	5.75, 7.30	
Creatinine (2838)			<0.0001
creatinine <1 (ref)			
1<=creatinine <1.5	0.61	0.55, 0.67	
1.5<=creatinine <2	0.62	0.52, 0.76	
creatinine >=2	1.23	1.01, 1.49	
WBC (2839)			<0.0001
WBC<12 (ref)			
WBC>=12	3.37	3.00, 3.79	
HgB (2776)			<0.0001
HgB>13 (ref)			
10<=HgB<=13	1.84	1.62, 2.08	
Hgb<10	4.28	3.75,4.89	
BMI (2841)			<0.0001
BMI <18.5	1.75	1.50, 2.04	
18.5<=BMI<25 (ref)			
25<=BMI<30	0.65	0.58, 0.73	
BMI>=30	0.55	0.48, 0.63	

We have undertaken significant assessments of the role of body mass index (BMI) on outcomes for immunotherapy recipients. This has been driven by research supporting the role of BMI as potentially predictive of toxicity events and survival from cancer immunotherapy. Significant findings to date have shown an association with a BMI > 30 (classified as obese) and improved overall survival. These findings are presented below in Figure 1 (Kaplan Meier assessment) and in Table 17 (representing a multivariate model with comorbidities and age as covariates).

Table 17: Multivariate Association with Overall Survival at 1 year

Parameter	Hazard Ratio	95% Hazard Ratio Confidence Limit
Obesity (BMI > 30)	0.402	0.200 - 0.809
Romano Comorbidity Score	1.085	0.993 - 1.186
Age	0.991	0.955 - 1.016

Figure 1: Overall Survival Among Immunotherapy Recipients by BMI within VA cohort



Initial findings from a retrospective analysis of a prospective study became available during the time of this grant's progress that impacted additional analyses. This paper (Qian et al. *Effect of immunotherapy time-of-day infusion on overall survival among patients with advanced melanoma in the USA (MEMOIR): a propensity-score matched analysis of a single-centre, longitudinal study.* Lancet Oncol. 2021 Dec;22 (12) 1777-1786) found that time-of day of checkpoint inhibitor infusion was potentially associated with improved overall survival. This was not an initial potential candidate predictor of overall survival or immunotherapy toxicity that we had considered, but the findings of the paper noted above led us to initiate an initially brief analysis that has opened additional avenues of investigation within the umbrella of this grant. We initially performed univariate analyses of 1 and 2 year OS with time of day and findings are presented below in Table 18 and Table 19.

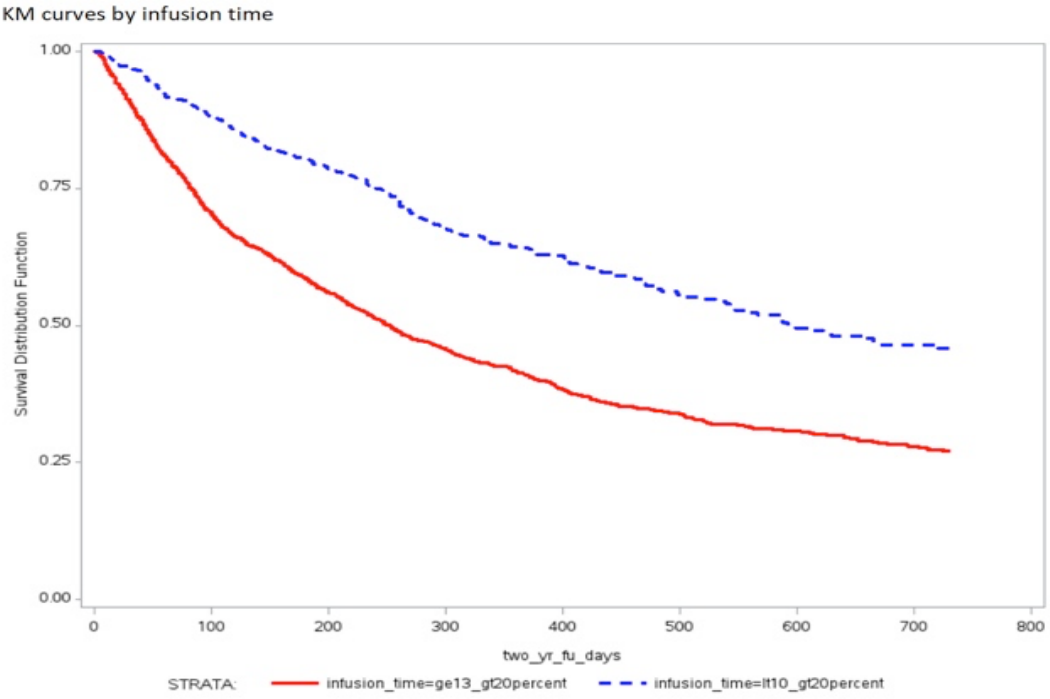
Table 18: Impact of Early Checkpoint Inhibitor Infusion (Before 10AM) vs Late Infusion (After 1PM) on Overall Survival (OS)

Disease	1 Year OS Hazard Ratio	95% Confidence Interval	P-Value
Lung Cancer (NIVOLUMAB ONLY)	1.947	1.391 - 2.726	0.001
Kidney Cancer	0.951	0.489 - 1.848	0.8817
Head and Neck Squamous Cell Carcinoma	2.574	1.579 - 4.194	0.0001
Bladder Cancer	2.359	1.367 - 4.072	0.0021
Melanoma	5.38	1.667 - 17.364	0.0049

Table 19: Impact of Early Checkpoint Inhibitor Infusion (Before 10AM) vs Late Infusion (After 1PM) on Overall Survival

Disease	2 Year OS Hazard Ratio	95% Confidence Interval	P-Value
Lung Cancer (NIVOLUMAB ONLY)	1.634	1.217 - 2.192	0.001
Kidney Cancer	1.119	0.621 - 2.017	0.7076
Head and Neck Squamous Cell Carcinoma	2.433	1.531 - 3.868	0.0002
Bladder Cancer	2.082	1.292 - 3.355	0.0026
Melanoma	3.721	1.482 - 9.344	0.0051

Figure 2: All Diagnoses, Overall Survival By Infusion Time (BLUE = 50% of infusions before 10AM, RED = 50% of infusions after 1PM



We additionally performed an exploratory analysis of OS looking at percentage of early (before 10AM) versus late (after 1PM) checkpoint inhibitor infusions, including in this analysis ALL diagnoses. The results of this uncorrected Kaplan Meier analysis is presented in Figure 2 above. Findings of both the univariate analyses by disease state and the general analysis of all diagnoses were significant. This caused us to look deeper into additional analyses looking at time of infusion, including significant interest in whether this impacts toxicities. Concerns about the potential for confounders leading to this observed difference in OS led to additional analyses, including evaluation of the differences in patient characteristics among early versus late treatment recipients and disease specific cohort assessments.

Table 18: Demographic Data for ALL diagnoses, with > 50% EARLY (<10AM) vs >50% LATE (>1PM) infusion

Table 18: Demographic Data for ALL patients EARLY vs LATE Treatment

	Total (N=2544)		
Demographic clinical characteristics	early treatment n=1729	late treatment n=815	P-value
Age (mean years)	68.5	68.8	0.43†
Male (%)	97.1	95.8	0.09*
Charlson score index (mean)	4.4	4.7	0.08†
Race (%)			0.08*
White	83.5	80.7	
non-whtie	16.5	19.3	
BMI categroy (%)			0.049*
BMI<18.5	5.5	7.9	
18.5<=Bmi<25	41.1	43.2	
25<=Bmi<30	30.9	29.1	
BMI>30	22.5	19.8	

* Chi-square test

† T-test

The demographic data as above in Table 18 of early versus late treatment showed no significant differences between patient characteristics for early versus late infusion times. As a result of this analysis we looked at Lung cancer as our test case, given it is the largest cohort for analysis. Demographics of early vs late infusion was assessed in Table 19 below. Once again there was little difference in significant features of patients between early and late cohorts. As in Figure 3, uncorrected Kaplan-Meier analyses showed improved OS with early infusion (defined here as < 1PM vs > 1PM). With a goal to control for potential confounders, we performed propensity score matched analyses on the Lung and Melanoma cohort as well as multivariate COX proportional hazards model analysis on these cohorts. These data are presented in Table 20 and 21 below as well as Figures 4 and 5. The ongoing benefit of early infusion with respect to OS was preserved in all of these analyses, including propensity score matching on age and comorbidities.

Table 19: Demographic features of early vs late treatment in Lung Cancer Cohort

Table 19: Demographic for lung cancer between early vs. late treatment: LUNG CANCER

Demographic clinical characteristics	Total (N=1451)		P-value
	early treatment n=1004	late treatment n=447	
Age (mean years)	68.8	68.7	0.94†
Male (%)	96.1	95.5	0.60*
Charlson score index (mean)	4.4	4.6	0.36†
Race (%)			0.12*
White	81.2	77.6	
non-whtie	18.8	22.4	
BMI categroy (%)			0.13*
BMI<18.5	4.7	7.4	
18.5<=Bmi<25	44.3	46.1	
25<=Bmi<30	31.2	27.7	
BMI>=30	19.8	18.8	

* Chi-square test

Figure 3: Kaplan Meier Overall Survival Analysis By Infusion Time (> 50% before 1PM vs > 50% after 1PM): Lung Cancer Cohort

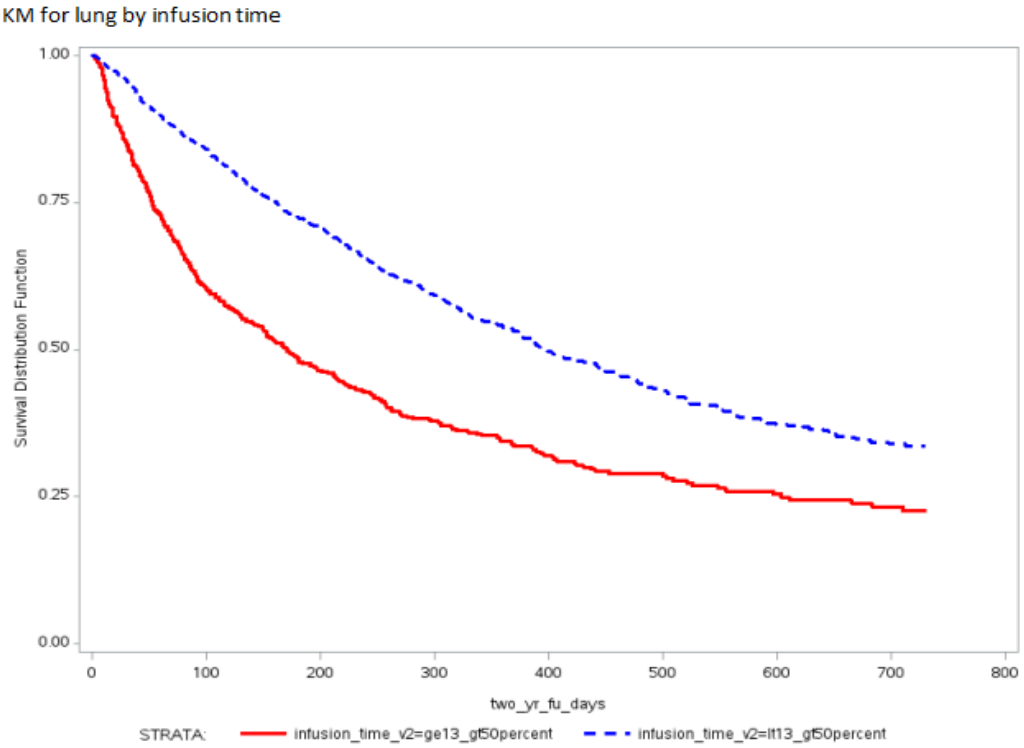


Table 20: Propensity Score Matched Lung Cohort COX analysis, Controlling for comorbidities, age, BMI, and Race, Two Year

Parameter	2 Year OS Hazard Ratio	95% Confidence Interval	P-Value
Infusion Time After 1PM (compared to before 10AM)	1.546	1.312 - 1.821	<0.0001
Age	1.01	0.999 - 1.021	0.0848
Race (Caucasian vs Non-Caucasian)	1.157	0.939 - 1.427	0.1716
BMI below 18.5	1.294	0.944 - 1.776	0.1097
BMI between 25 - 30	0.782	0.645 - 0.949	0.0128
BMI between 30 - 35	0.629	0.481 - 0.823	0.0007
BMI greater than 35	0.627	0.426 - 0.923	0.0179
Romano Comorbidity Score	1.043	1.015 - 1.071	0.0022

Table 21: Demographic features of Early versus Late Infusion Time Among Melanoma Cohort (Propensity Score Matched)

Table 21: Demographic for melanoma between early vs. late treatment

Demographic clinical characteristics	Total (N=292)		P-value
	early treatment n=188	late treatment n=104	
Age (mean years)	68.7	69	0.82†
Male (%)	98.9	93.3	0.007*
Charlson score index (mean)	3.3	3.8	0.15†
Race (%)			0.01*
White	97.9	91.4	
non-whtie	2.1	8.6	
BMI categroy (%)			0.16*
BMI<18.5	2.1	1.9	
18.5<=Bmi<25	23.4	35.6	
25<=Bmi<30	36.7	32.7	
BMI>=30	37.8	29.8	

* Chi-square test

† T-test

Table 22: Propensity Score Matched Melanoma Cohort COX analysis, Controlling for comorbidities, age, BMI, and Race, Two Year OS

Parameter	2 Year OS Hazard Ratio	95% Confidence Interval	P-Value
Infusion Time After 1PM (compared to before 10AM)	2.562	1.667 - 3.938	<0.0001
Age	1.004	0.984 - 1.025	0.6956
Race (Caucasian vs Non-Caucasian)	0.708	0.320 - 1.567	0.3948
BMI below 18.5	2.147	0.483 - 9.531	0.3152
BMI between 25 - 30	0.684	0.419 - 1.116	0.1281
BMI between 30 - 35	0.542	0.290 - 1.014	0.0553
BMI greater than 35	0.911	0.498 - 1.665	0.7613
Romano Comorbidity Score	1.019	0.951 - 1.092	0.5975

Given these findings, we did discuss with the basic science division at Washington University in St. Louis, regarding the potential underlying Biological rationale for this observed association of OS with a team of Chronobiologists. Given the long half-life of immune checkpoint inhibitors (weeks in most cases) and the typical treatment course being declared either successful or a failure after several cycles of treatment (typically 3-4) we decided to investigate the timing of the initial dose of immunotherapy as a predictor event.

Figure 4: Lung cancer OS by Time of First Checkpoint Inhibitor Infusion: 10AM or earlier (red) vs after 1PM

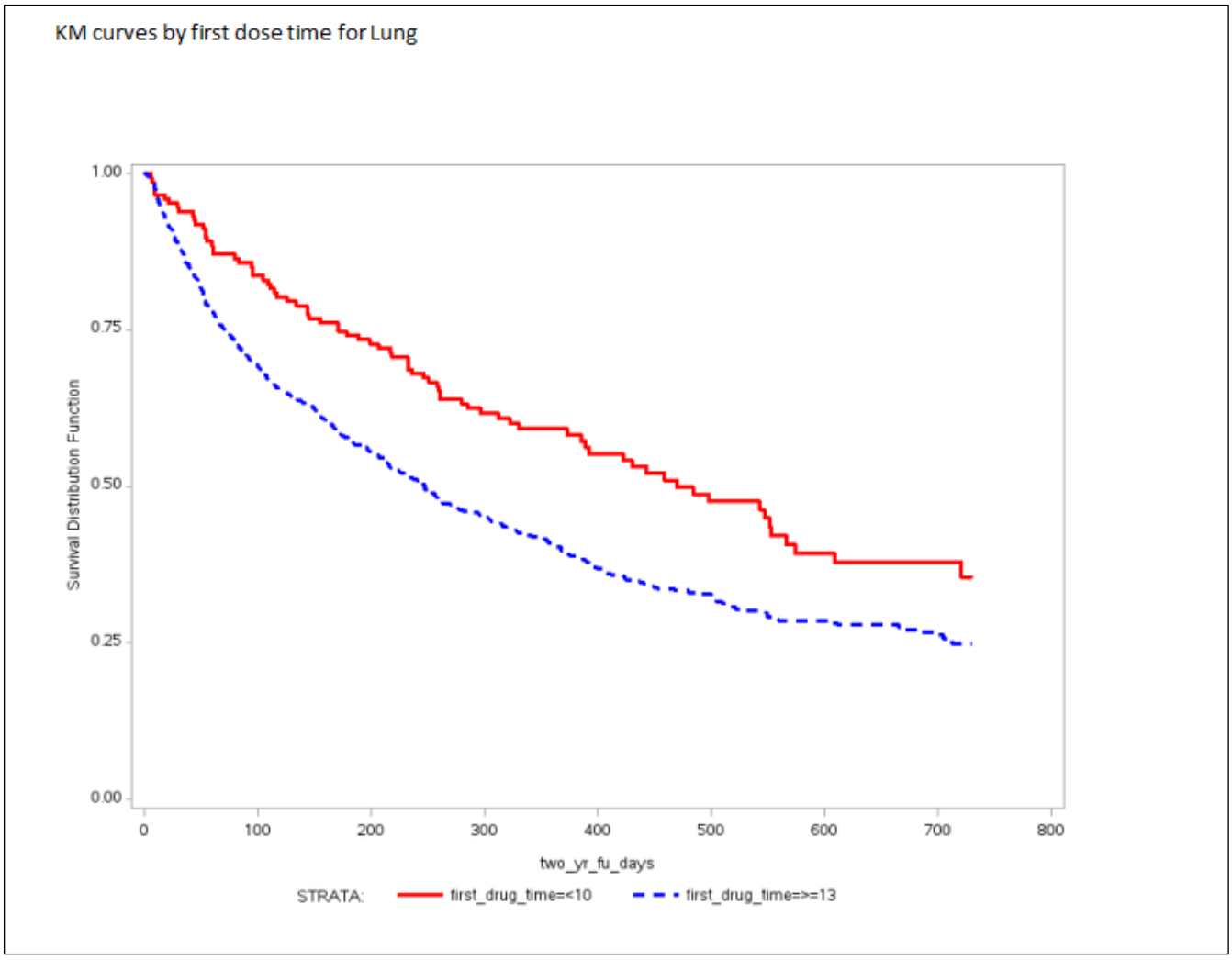
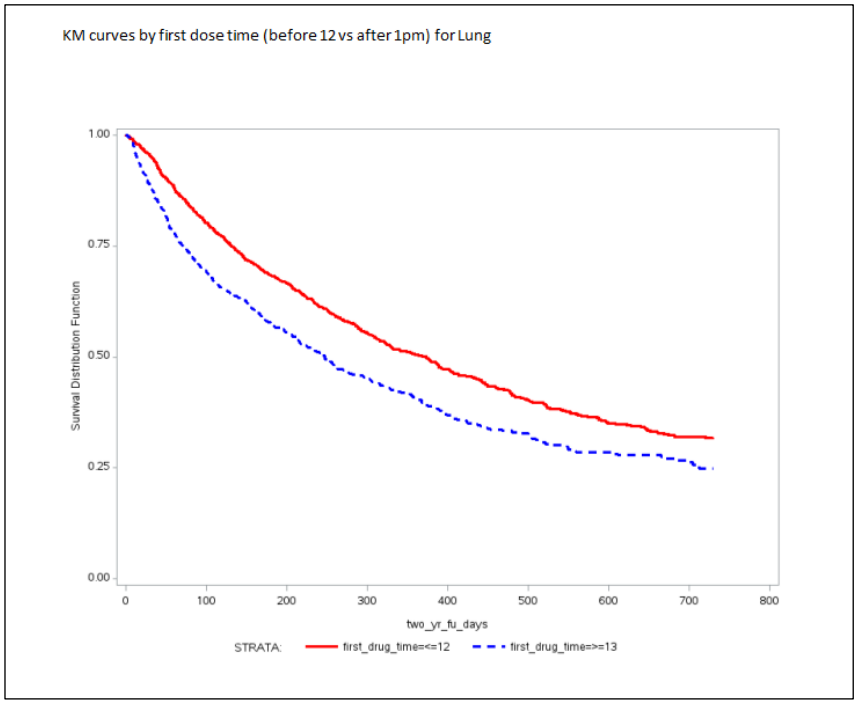


Figure 5: Lung cancer OS by Time of First Checkpoint Inhibitor Infusion: 12PM or earlier (red) vs after 1PM



We also investigated similar treatment times and outcomes in the Melanoma cohort. This is seen below in Figure 6 and Figure 7.

Figure 6: Melanoma OS by Time of First Checkpoint Inhibitor Infusion: 12PM or earlier (red) vs after 1PM

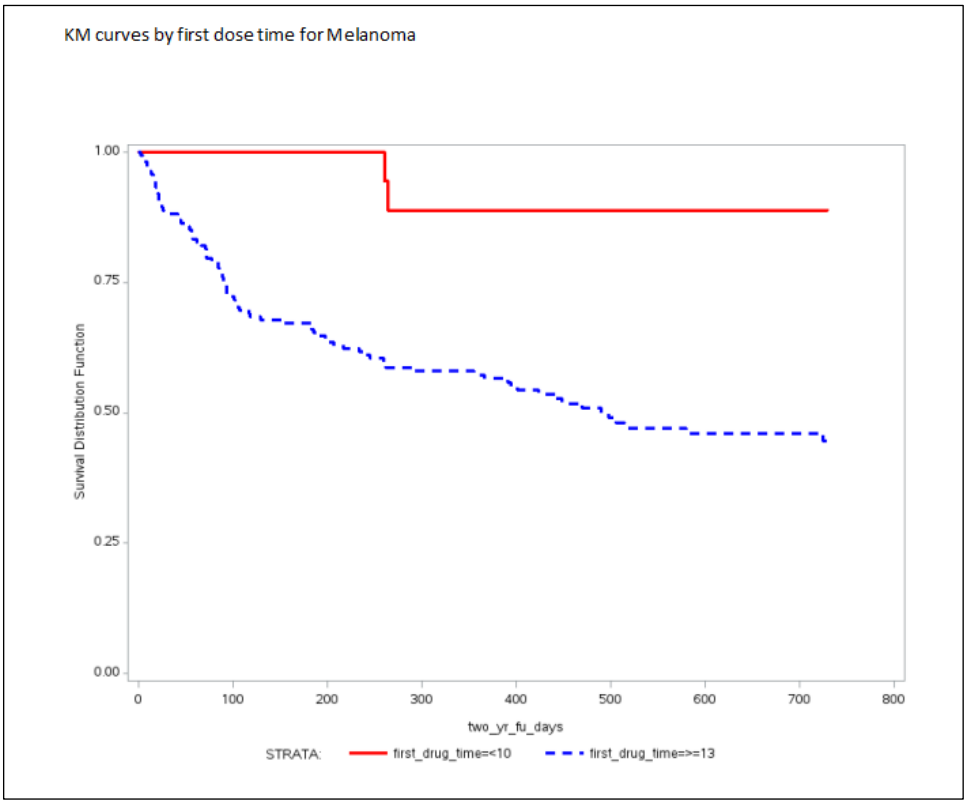
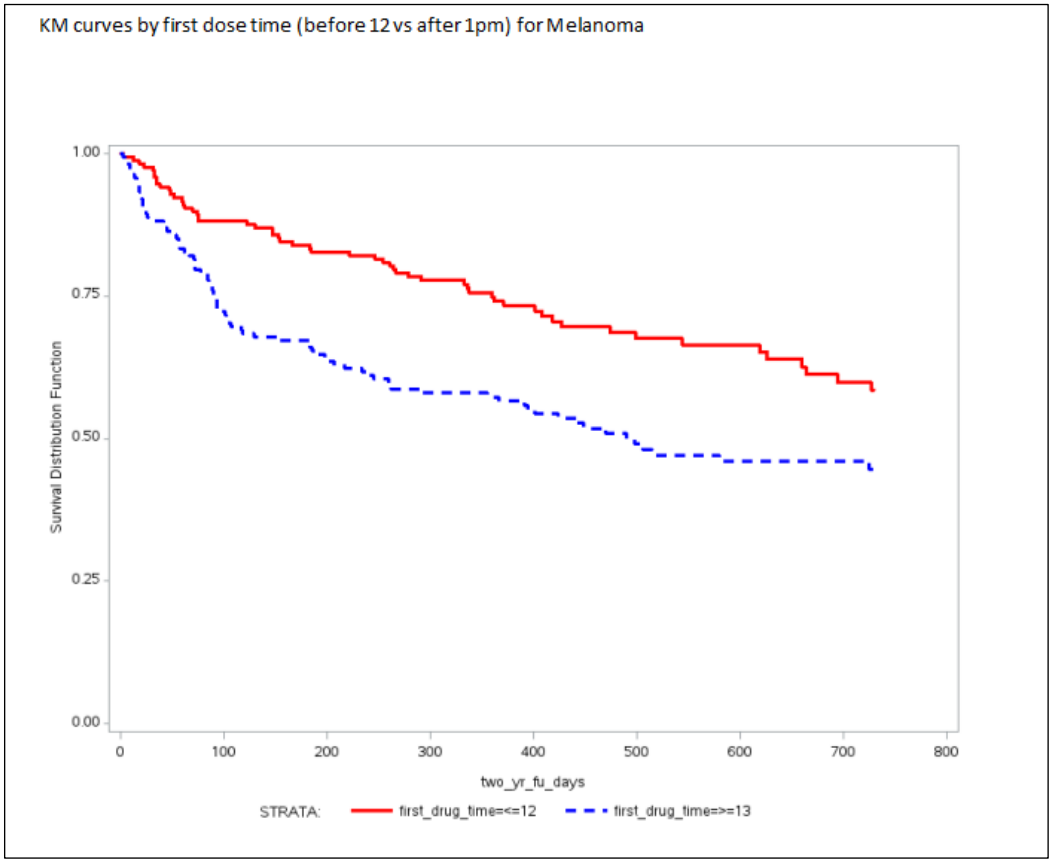


Figure 7: Melanoma OS by Time of First Checkpoint Inhibitor Infusion: 12PM or earlier (red) vs after 1PM



Expanding on these analyses we aimed to correct for the impact of frailty and potential difficulties with travel to and from the center by adjusting in multivariate models for distance from the treating center and utilizing a frailty score that was developed at our VA Research Center (Patel et al. *Frailty in Older Adults with Multiple Myeloma: A Study of US Veterans.* JCO Clin Cancer Inform. 2020 Feb;4:117-127). After inclusion of this scoring systems into the multivariate model and adding distance to the treating center, there was persistence of the survival advantage for early infusion time. A Propensity Score Matched model was created for Lung CA, Melanoma, Head & Neck SCC and Bladder cancer, controlling for age, comorbidities, distance to treating center and frailty, findings were positive in most disease states (all were negative in Renal Cell Cancer). Findings are presented below in Table 23.

Table 23: Time of 1st ICI infusion and OS, Propensity Score Matched COX Model, Controlling for Age, Frailty, and Distance

Disease	Hazard Ratio for 1 Year OS	Hazard Ratio for 2 Year OS
Lung Cancer	1.446 (1.028 - 2.032)	1.656 (1.22 - 2.243)
Melanoma	4.987 (1.593 - 15.608)	2.960 (1.143 - 7.663)
Head and Neck SCC	1.694 (0.947-2.948)	2.525 (1.499 - 4.252)
Bladder Cancer	2.582 (1.388 - 4.803)	2.049 (1.230 - 3.414)

At this time we are writing up the findings as presented above regarding checkpoint inhibitor timing and improve Overall Survival. We hope to have this published within the next several months.

- ***Subtask 4: Exclusion of covariate pairs with strong correlation in VA dataset***
  - **Initial analyses have not revealed significant correlation among covariate pairs within candidate predictors, but this is an ongoing assessment.**
- ***Subtask 5: Multivariate analysis and finalization of the model in VA dataset***

Table 24 presents an initial multivariate model for risk factors associated with Prednisone prescription from the VA dataset. These will serve as potential predictors in the final model. Additional work is proceeding on this portion of the study.

Table 24: Multivariate association with Prednisone Prescription (Autoimmune Toxicity) in VA cohort

Effect	Odds Ratio Estimate	95% Confidence Interval
BMI (BMI < 18.5 vs BMI 18.5 - 25)	0.633	0.394 - 1.019
BMI (BMI 25 - 30 vs 18.5 - 25)	1.092	0.848-1.406
BMI (BMI 30 - 35 vs 18.5 - 25)	1.557	1.141-2.123
BMI (BMI > 35 vs BMI 18.5 - 25)	1.291	0.853-1.955
Hemoglobin (10-13 vs >13)	0.872	0.692-1.101
Hemoglobin (<10 vs >13)	0.506	0.355 - 0.722
Albumin (3-3.5 vs >3.5)	0.941	0.737 - 1.202
Albumin (< 3 vs > 3.5)	0.681	0.497 - 0.932
Diabetes Mellitus	0.736	0.588 - 0.920
Renal Disease	1.607	1.056 - 2.446
Lung Disease	1.315	1.034 - 1.673
Nivolumab Use	0.729	0.529 - 1.003
Pembrolizumab Use	0.659	0.477 - 0.910
Atezolizumab Use	0.506	0.295-0.865

- ***Subtask 6: Validation of the model utilizing WUSTL dataset***
  - **Work on this Subtask is ongoing currently. Delays in abstraction and confirmation of Prednisone prescription as a predictor of autoimmune toxicity (now complete) delayed work on this until the present time.**

MAJOR TASK 4: *To develop a machine learning based risk prediction model*

Task Overview: The bulk of this task is still sometime in the future, and work continues on the process of setting up the model, denoting and cleaning the data, as well as appropriately identifying autoimmune toxicity events so that the model is accurate and effective. We have developed the basic framework for the model at this time and have run a preliminary attempt at model derivation. Initially, we had planned to use the *Autoprognosis* python model to develop the machine learning model, but we have abandoned this approach to

utilize more traditional protocols in model development. This is mainly due to increased machine learning expertise among our research staff (Dr. Inez Oh).

- ***Subtask 1: Cleaning/Denoting dataset for ML protocols***
    - **We have completed cleaning and denoting of the dataset for ML protocols and have results from ML analyses on the Washington University in St. Louis cohort.**
- ***Subtask 2: Utilization of Autoprognosis python module to develop ML mode***
    - **We have moved on from Autoprognosis and are using pure Python based approaches to implement ML analyses.**
- ***Subtask 3: Utilization of manual ML protocols to develop routine ML model***
    - **Given improvement in ML capabilities we are using Python based approaches to develop ML models and proceed with ML analyses.**

Initial ML models for predictors of irAEs and Overall Survival at 1 and 2 years are presented below. In Table 25 and 26, candidate models and predictors are presented. In Figure 8, a Machine Learning Random Forest model is presented showing predictors of autoimmune toxicity. These are presented in Shapley Additive Explanation (SHAP) plots. Figure 9 displays a K-nearest neighbor (KNN) model of autoimmune toxicity development. In these plots, more important features (variables) are higher in the list. Figures 10-11 present a model for risk of death at 1 year via a logistic regression and xtree model. Figure 12-13 presents a model for risk of death at 1 year via a logistic regression and xtree model. These are key intial ML models for prediction of overall survival and immune toxicity development.

Table 25: Machine Learning Model Approaches Utilized

ML Models Utilized
Parameter Grid-Search
5-fold cross-validation
Logistic Regression
Decision Tree
Random Forest
Extra Trees
Gradient Boosting Classifier
K-nearest Neighbors

Table 26: Sample Features assessed in ML Models

Features Utilized in Model
Sex
BMI
Race
Cancer Diagnosis
Checkpoint Inhibitor
Creatinine
Hemoglobin
Albumin
MI
Hepatitis
HF
PVD
Renal Disease
HIV
Liver Disease
Diabetes
COPD

Figure 8: ML Model Feature Components (SHAP Plot) iRAE Development, Random Forest Model

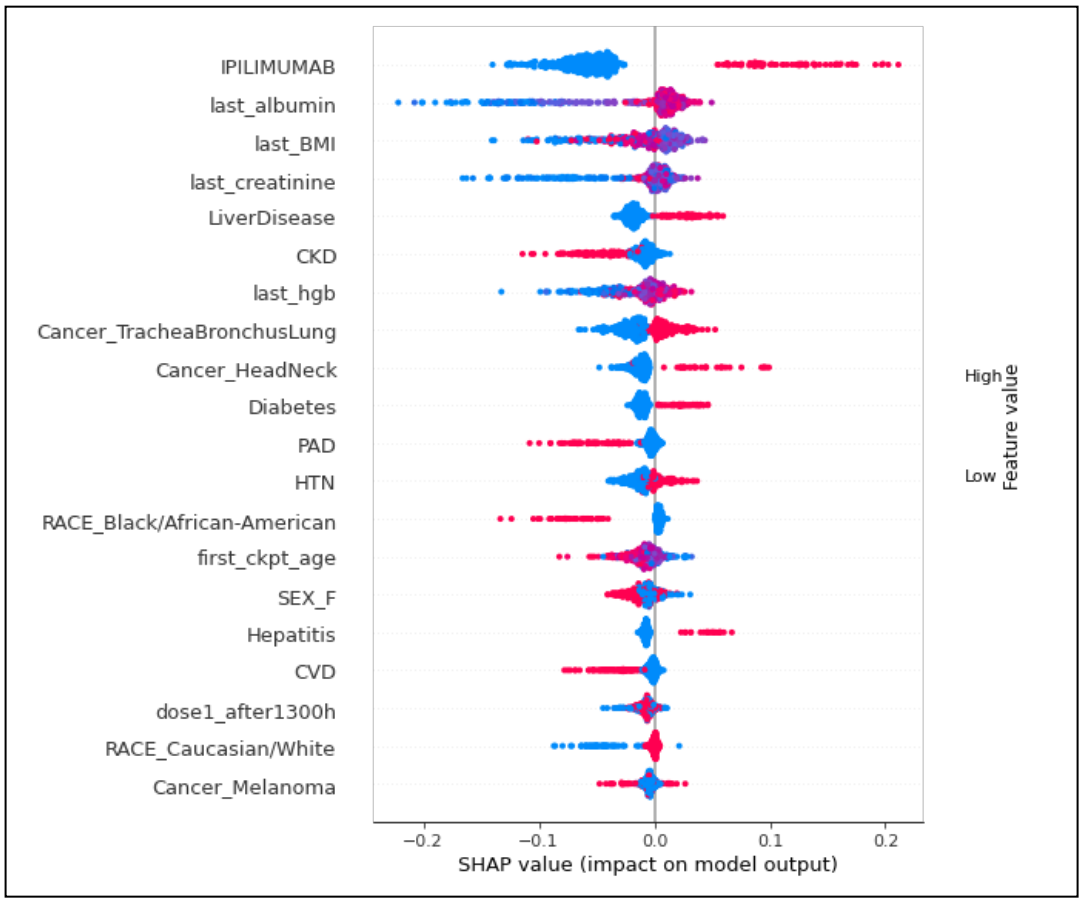


Figure 9: ML Model Feature Components (SHAP Plot) iRAE Development, KNN Model

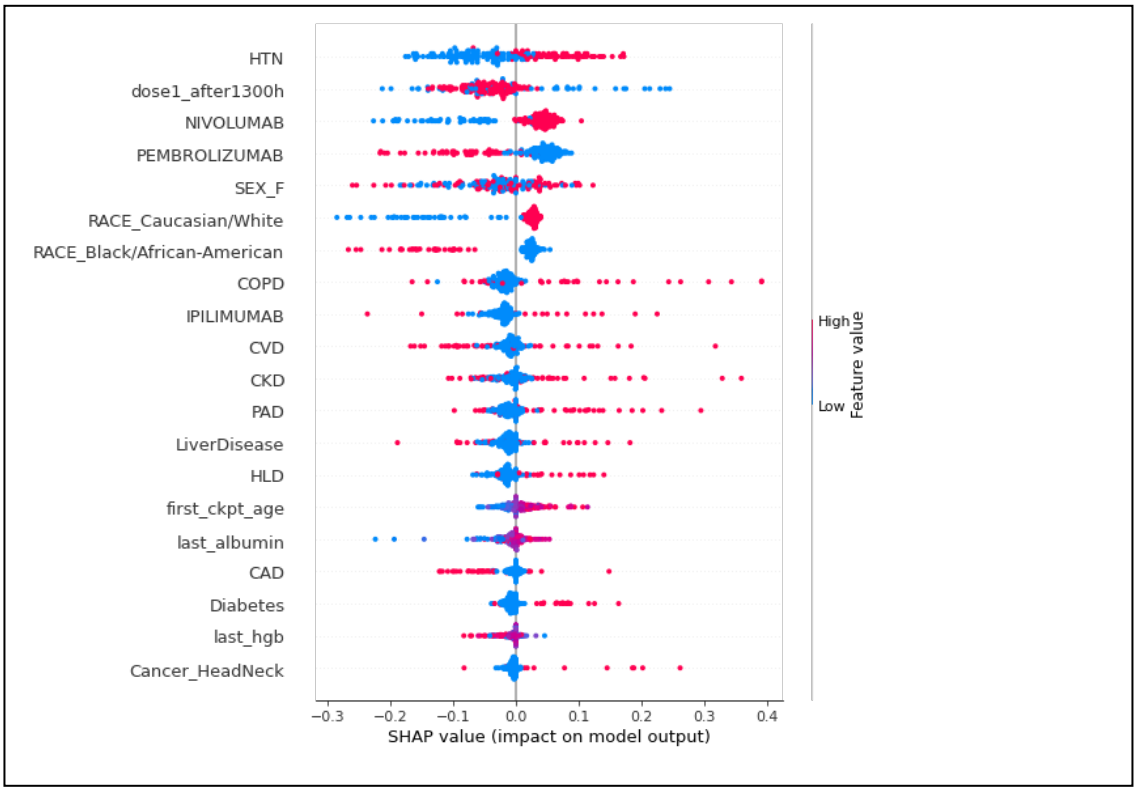


Figure 10: ML Model Feature Components (SHAP Plot) Death at 1 Year, Logistic Regression Model

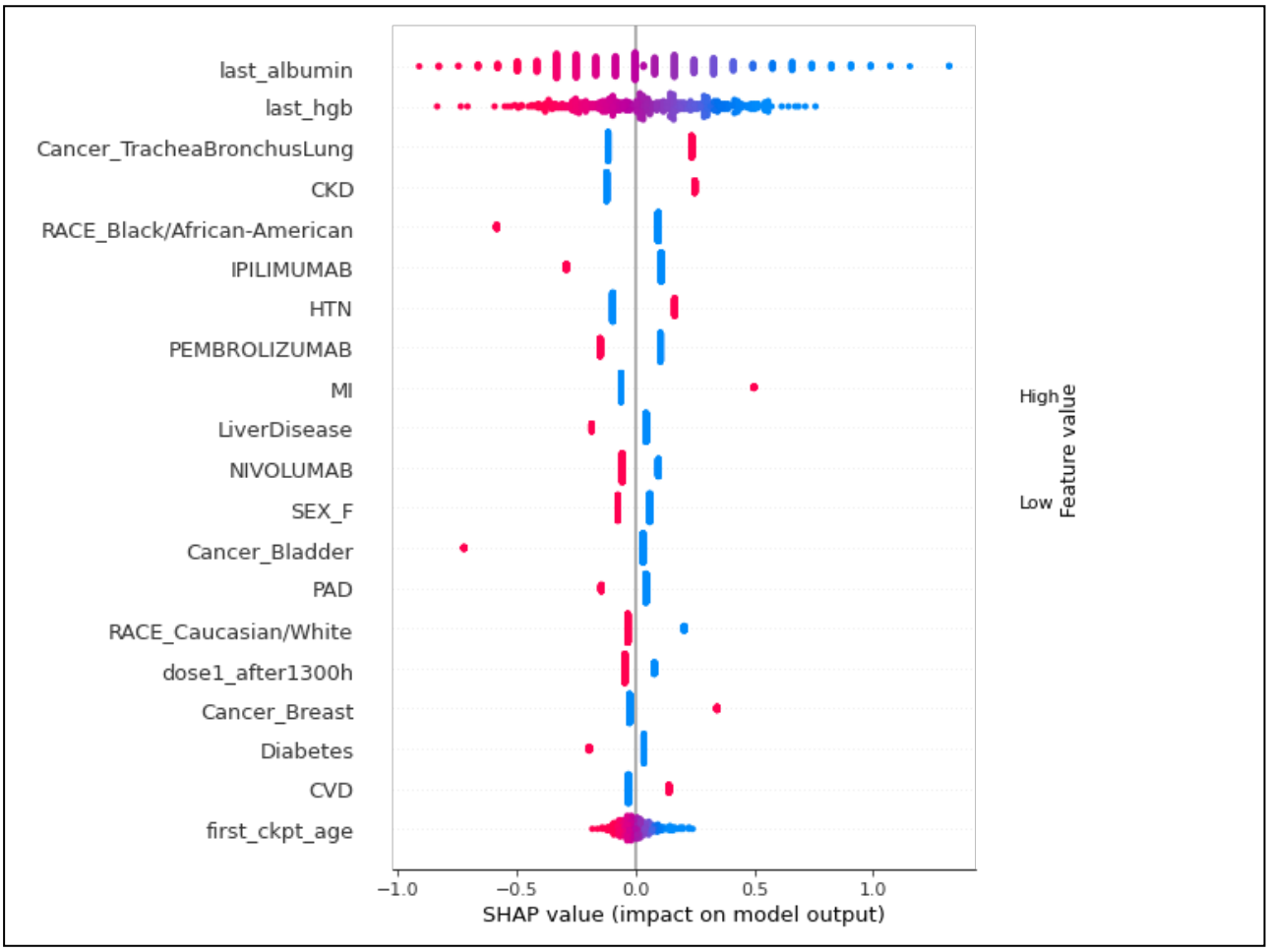


Figure 11: ML Model Feature Components (SHAP Plot) Death at 1 Year, XTREE Model

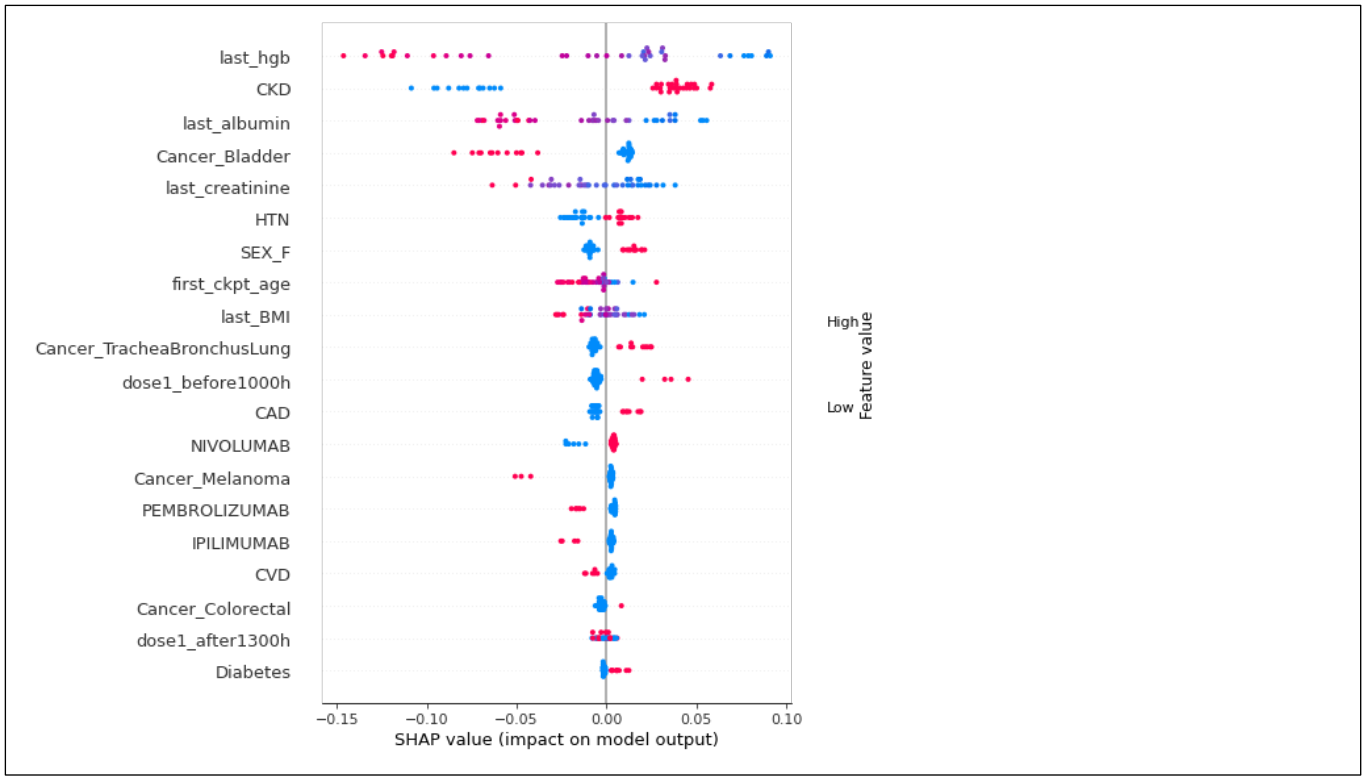


Figure 12: ML Model Feature Components (SHAP Plot) Death at 2 Years, Logistic Regression Model

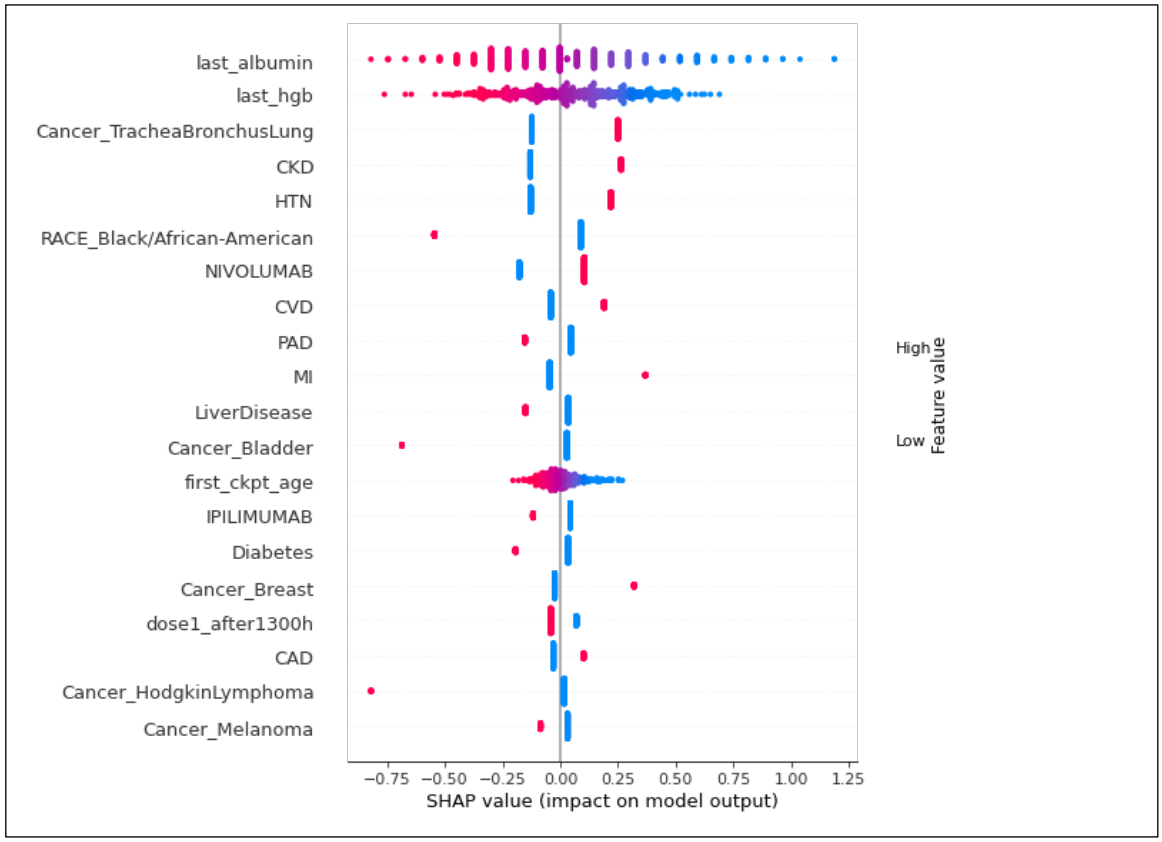
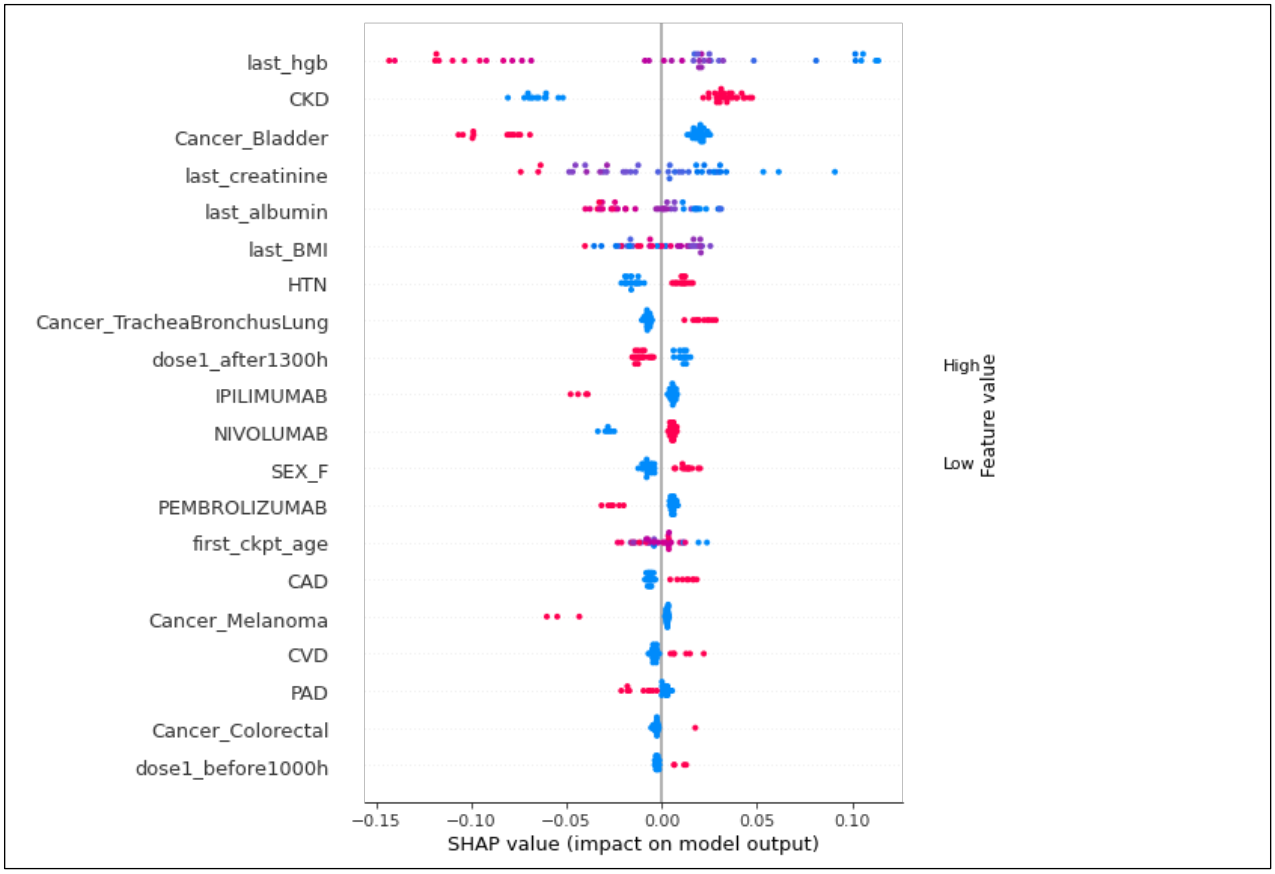


Figure 13: ML Model Feature Components (SHAP Plot) Death at 2 Years, XTREE Model



- ***Subtask 4: Comparison of ML models (Autoprognosis vs Routine)***
    - **This task is no longer necessary given our approach of utilizing pure Python routines as opposed to Autoprognosis.**
- ***Subtask 5: Validation of optimal ML model with WUSTL data***
    - **Wea have made substantial progress on this approach. We are currently evaluating models presented above in Figures 8-13 to find the optimal model for prediction of irAEs and OS.**
- ***Subtask 6: Comparison of optimal ML model with Regression based model***
    - **This task is ongoing and pending completion of other associated and dependent tasks.**
- ***Subtask 7: Preparation of manuscript and publication of results***
    - **Some manuscripts have been submitted as detailed in Appendix.**

MAJOR TASK 5: *To correlate development of autoimmune toxicities with PFS and OS as compared to those not developing toxicity*

- ***Subtask 1: Calculate OS utilizing disease specific survival data***
    - **We have completed OS calculations for cohorts at the VA and WUSTL. These data are included and necessary for the models and calculations as above and will not be presented on their own.**
- ***Subtask 2: Calculate OS and PFS data for patients with grade 3/4 toxicities***
    - **We have calculated OS data for patients with grade 3/4 toxicities from ICI therapy as identified by various mechanisms, including ICD codes and Prednisone prescriptions.**

Figure 14: Overall Survival for all cancer diagnoses from VA data among Prednisone recipients (autoimmune toxicity) vs No Prednisone

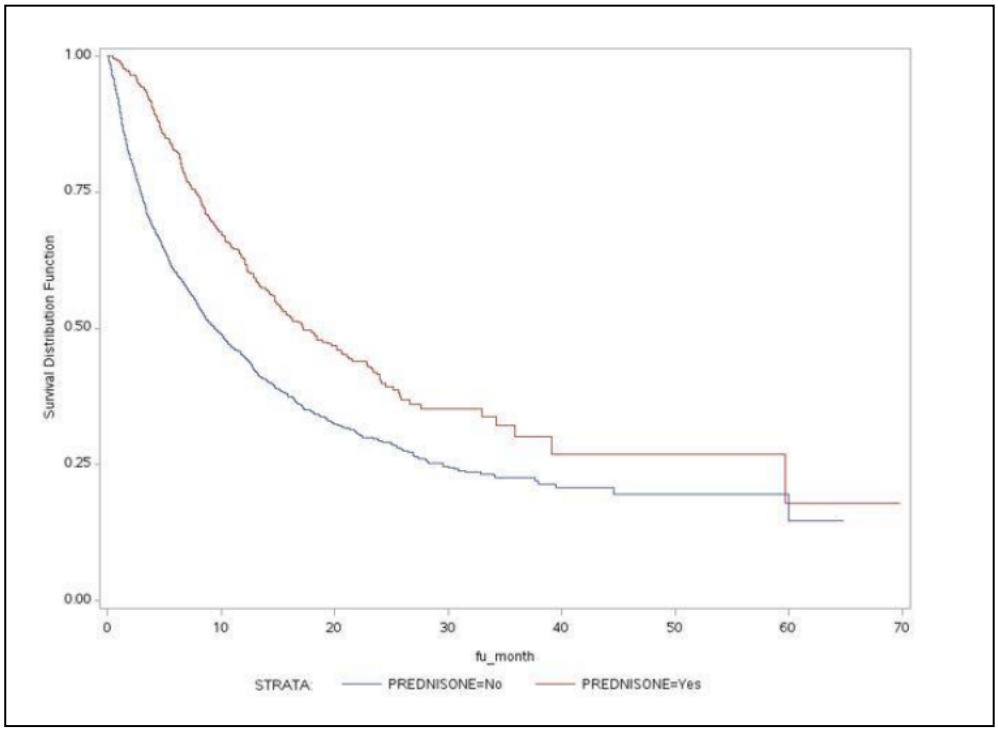
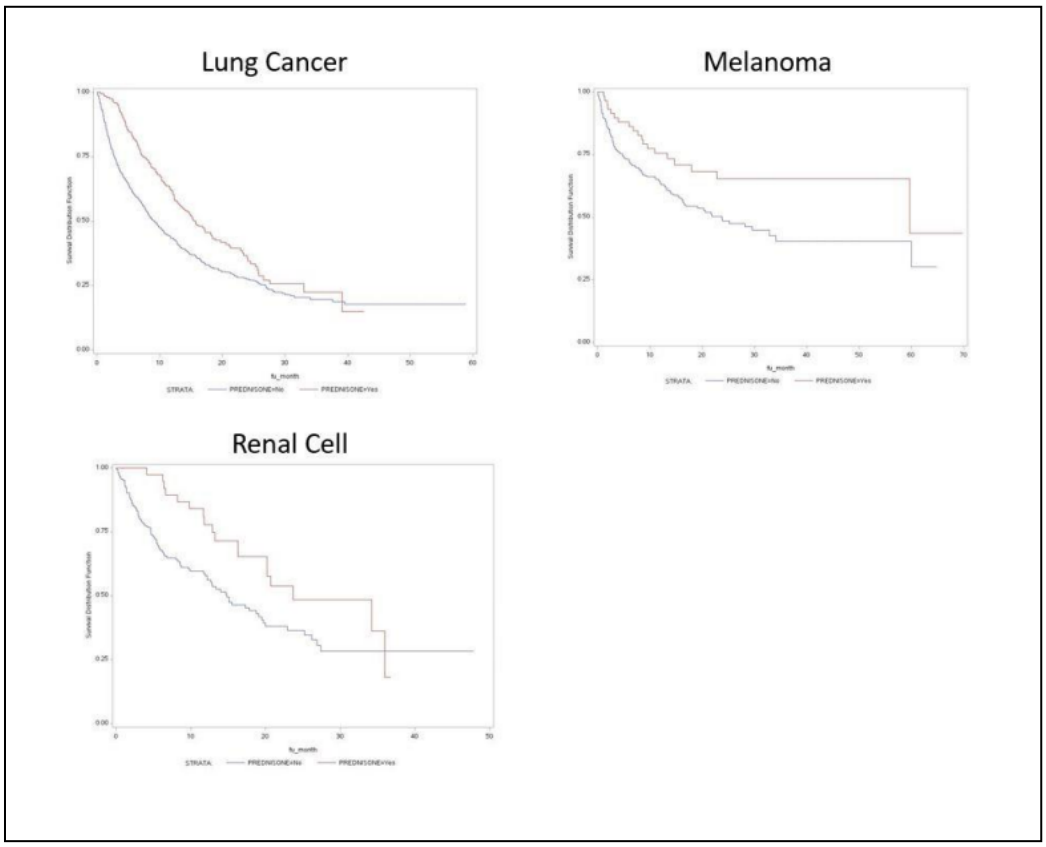


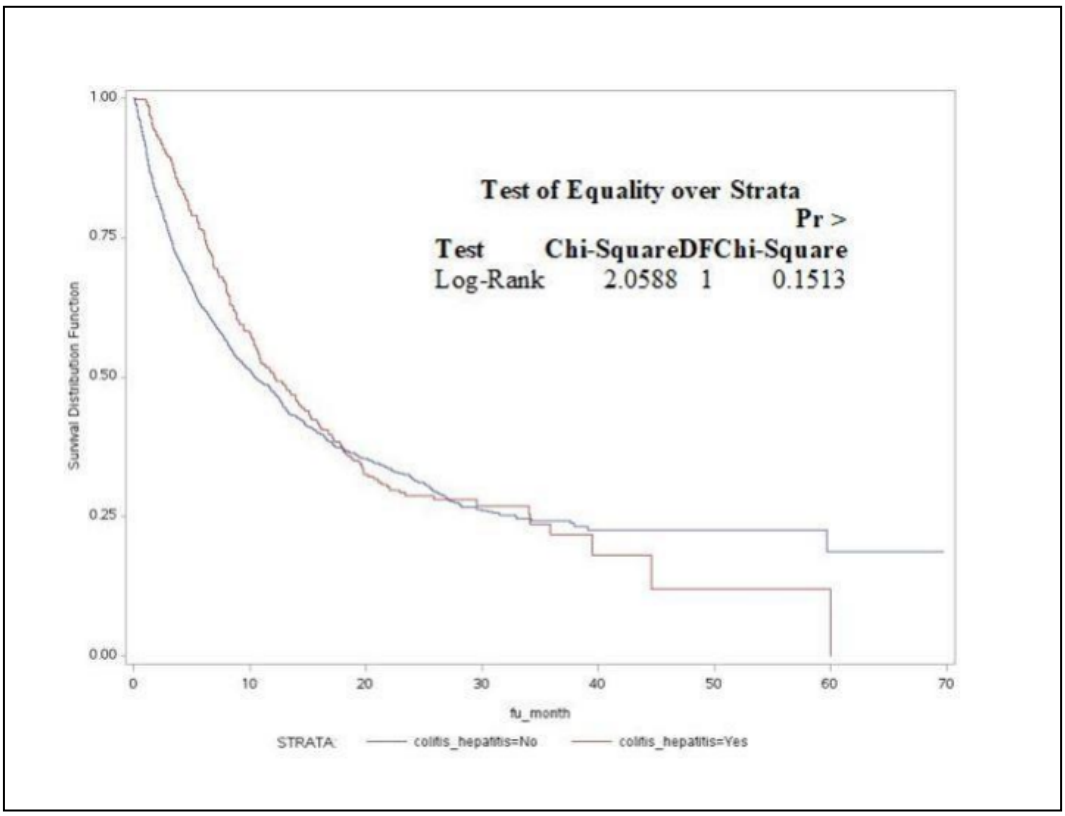
Figure 14 above shows a Kaplan-Meier survival analysis for patients from all cancer diagnoses who received ICI therapy, comparing those patients who received a prescription of prednisone during or within 6 months of completion of ICI treatments versus those who did not. Improved OS was observed and was statistically significant for patients receiving a prednisone prescription between the initial dose of ICI therapy and 6 months post ICI therapy concluded.

Figure 15: Overall Survival for Lung, Melanoma and Renal Cell among VA patients receiving Prednisone vs Not



Above in Figure 15, the findings outlined in Figure 2 are examined for key cancer diagnoses of melanoma, lung cancer and renal cell carcinoma. Findings here all support an improvement in overall survival for patients receiving steroid therapy during ICI treatment. This supports the association of immune related adverse events with improved survival among these cancer patients.

Figure 16: Overall survival for all diagnoses with toxicity event via ICD Codes, VA Data



Above in Figure 16, the effectiveness of ICD codes to identify toxicity events is assessed via a survival analysis among all cancer diagnoses, who had a recorded ICD code for a toxicity event during ICI therapy and up to 6 months post ICI therapy. As noted here, the survival is not different among these cohorts, suggesting potentially that ICD codes are not identifying toxicity events as well as prednisone therapy. Additional analyses to assess this finding are ongoing.

Below, in Figure 17, 1-year survival among all cancer diagnoses for patients with an ICD code defined toxicity event are presented. There is notable initial separation of survival curves early on in the survival analysis, suggesting potentially a short-lived effect on survival from an autoimmune toxicity.

Figure 17: All Diagnoses, 1 year survival by toxicity, VA Data

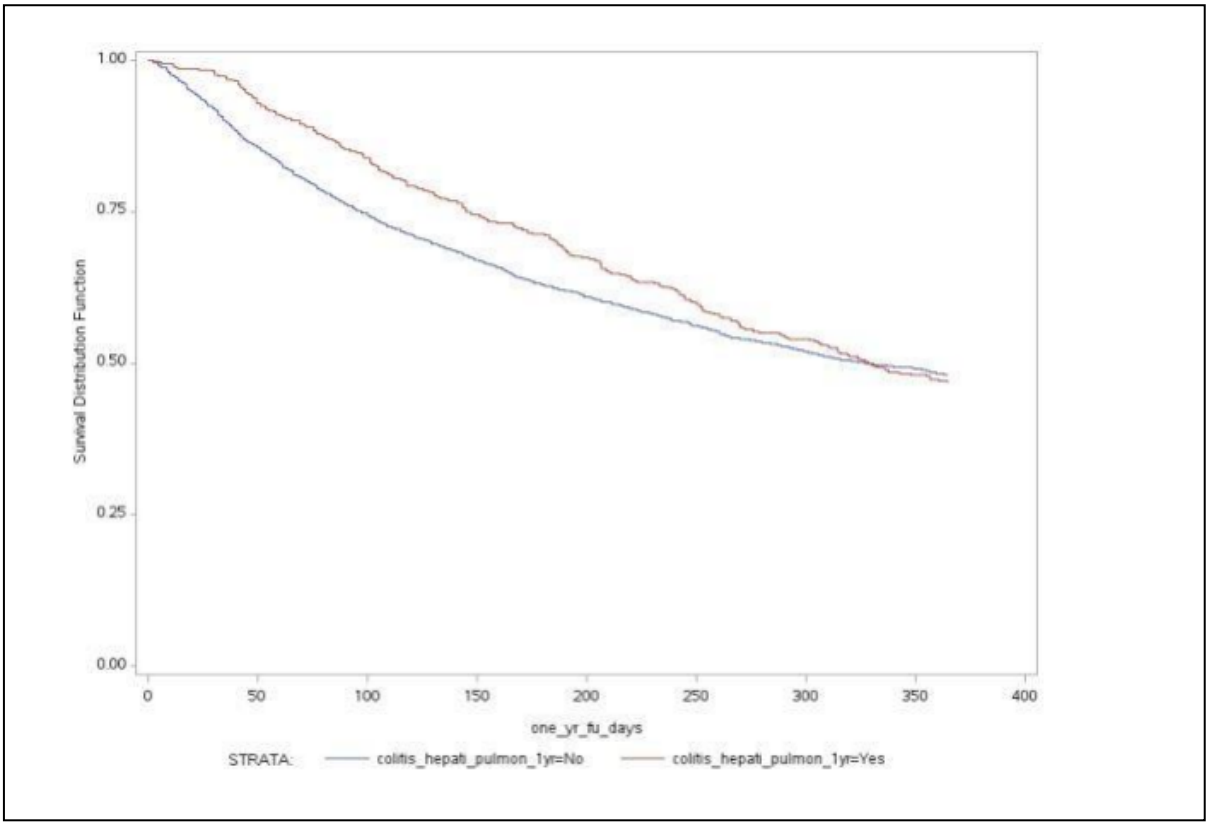
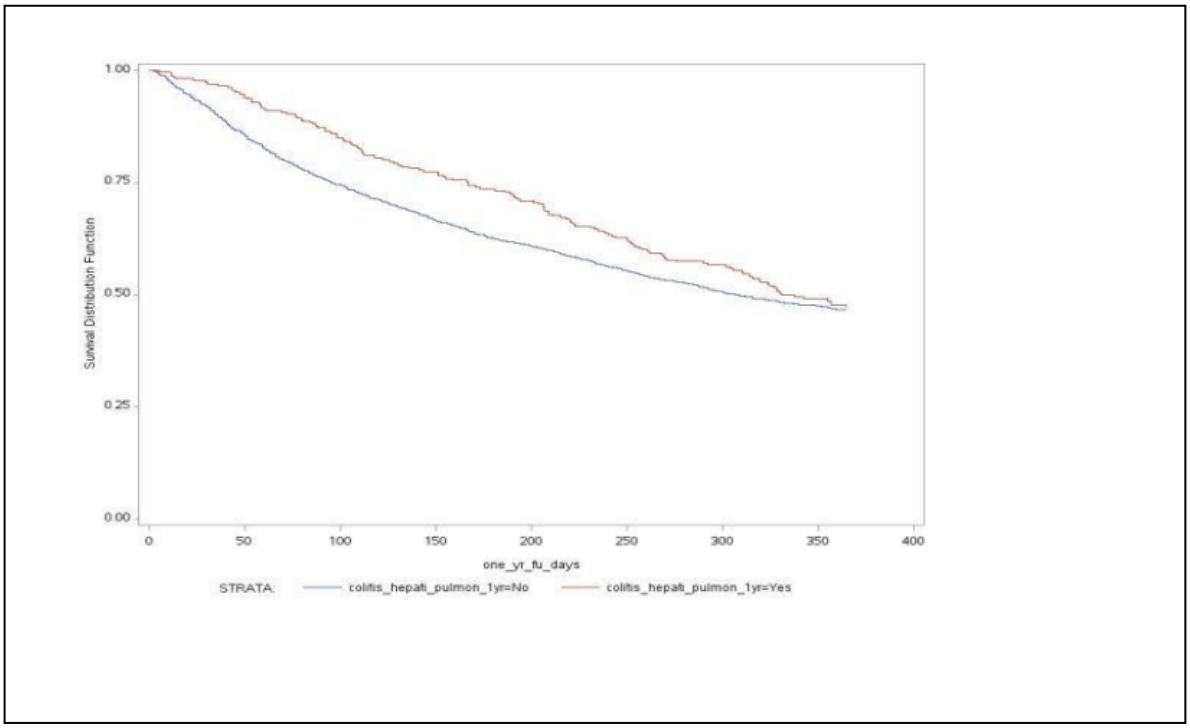


Figure 18: Overall survival among lung cancer patients among ICD code defined toxicity, VA Data



Above, in Figure 18, lung cancer patients were examined showing survival among patients with ICD code defined toxicity versus those without ICD code defined toxicity events.

- ***Subtask 3: Calculate and compare PFS data for patients with and without grade 3/4 toxicities, utilizing Kaplan-Meier methods***
    - **PFS has been a tough outcome to collect administratively and we have decided to limit the evaluation of PFS at this time. Abstraction allows PFS calculation, but has been time consuming and is not required for completion of alternate goals.**
- ***Subtask 4: Preparation and Publication of Manuscript***
    - **This is ongoing. Publications to date are included in the Appendix.**

4. Impact

***Current Impact*:** Currently, the impact is limited by the initial/early stage of the research project. We have already found significant and potential novel findings regarding BMI, and an association with improved overall survival among those receiving steroids while on ICI therapy. **Additionally the impact of the findings associated with time of infusion of ICI has the potential to be a very significant finding that may lead to additional grant funding and even prospective verification.** The finding of an association between steroid use during ICI therapy and improved survival suggests that adverse events are associated with significant improvement in clinical response and benefits. Furthermore, these findings suggest that the immunosuppression required to treat these adverse events do not eliminate the benefits from immunotherapy. **Additionally, we are eagerly analyzing the early results of the Machine Learning approaches to the WUSTL dataset and how to best proceed with additional evaluations of this cohort.**

Potential Clinical Impact: The final product of the research will have significant impact on the understanding of clinical outcomes surrounding cancer immunotherapy, autoimmune related adverse events, and prognostic markers in the modern era of ICI therapy.

5. Changes/Problems

***Problems/Challenges Encountered*:** There have been several challenges encountered during the initial year of the grant. We will review these in depth here as well as the planned approach to overcome these complications.

***Uncertain Utility of ICD Codes to Identify Autoimmune Toxicities*:** The publication of a study from Ohio State bv *Nashed, Zhang, et al*, showing the inaccuracy of ICD codes for the detection of autoimmune related adverse events highlighted the potential complications of utilizing ICD codes to identify immune related adverse events. The inability to distinguish autoimmune events without extensive abstraction is a limiting factor to the current project and other similar retrospective/administrative data projects. *Planned Solution*: The current plan is for an approach utilizing steroid prescriptions to identify autoimmune toxicity events. Anecdotally, our clinical experience informs us that ICD codes for complications of therapy are infrequently entered by treating clinicians, and utilizing a prescription as a marker of an event should be a much more reliable approach. In this manner we hope to find a more sensitive and specific tool for identifying immune related adverse events. **To date, this approach has been successful and has been shown to be a reasonable and appropriate option in our fully abstracted VA Melanoma cohort. We are working to show this to be an appropriate approach in other cohorts at this time.**

***Chart Abstraction*:** Complicating the efforts above, chart abstraction has been a more complicated and time-consuming effort than initially expected. The initial plan to utilize resident physicians to complete chart reviews was complicated by training and regulatory requirements (predominately at the Veterans Affairs hospital), as well as increased clinical demands from the COVID-19 pandemic. *Planned Solution*: **We continue to add new team members for abstraction and are moving forward as quickly as we can in this regard. It remains challenging. However, the demonstration of outpatient Prednisone prescriptions as an avenue of identification of autoimmune toxicities means that we can pivot to use this approach if delays continue.**

***COVID-19 Related Challenges*:** As noted above, COVID-19 has clearly impacted the study in numerous ways. Increased workloads among the research team has limited time spent on chart abstraction as well as statistical analysis and oversight. The limitations on group meetings has changed the nature of collaboration. For the most part, we have been able to catch up from initial delays in the research and are now well-positioned to move forward.

***Limitations of Washington University in St. Louis Dataset*:** The dataset at Washington University in St. Louis is a very robust dataset, but runs currently only from 2016 through mid-2018. This leaves out 3 years of potential additional patients treated with ICI therapy. **We have arranged via additional outside funding to extract an additional 3 years of data from the Washington University in St. Louis administrative databases, and we expect this will increase out patient dataset from Washington University to roughly 7000 patients. This will improve our ability to extract meaningful findings and increase the validity of our conclusions. This data was finally provided to us roughly 1 month ago and we are working to clean and prepare this data for additional analyses over the next several weeks/months.**

6. Products

***Final Product*:** The goal of this research and grant is to produce a risk prediction model for severe autoimmune toxicities from checkpoint inhibitor therapy among patients undergoing immunotherapy treatment for cancer. The utility of this tool will be significant, as it will allow clinicians to better counsel, select therapy and provide appropriate prognostic information for cancer patients. Additional goals of the research are to better explore predictors of toxicity, and predictors of overall survival among cancer patients.

***Progress Towards Final Product*:** As is outlined above under the Accomplishments section, significant progress has been made towards the goals of the grant. We have identified potential predictors of autoimmune toxicities and overall survival among cancer patients receiving immunotherapy. We have also made significant progress in the processing of our active datasets, as well as the training of our personnel to assist with ongoing research efforts. **We have found time of infusion to be a powerful predictor of OS among cancer patients receiving immune checkpoint inhibitors and are actively pursuing this unexpected discovery. This has the potential to open up new avenues of research in the coming months and beyond.**

***Publications*: Publications and abstracts are included in the addendum at this time. We are moving forward with publication of our findings regarding time of infusion of immune checkpoint inhibitors. We hope to have significantly more publications this year.**

7. Participants & Other Collaborating Organizations

***St .Louis Veterans Affairs Medical Center*:** The St. Louis VA Medical Center remains an ongoing and active research site for this grant. A brief review of resources is outlined below:

Clinical Facilities: The John Cochran VA Medical Center is a full-service, level I health care facility. It provides both inpatient and ambulatory care with over 65 subspecialties including hematology/oncology. We

are the largest hematology/oncology section in Missouri for Veterans to receive care. The majority of the patients served come from east central Missouri and southwestern Illinois.

Research Division: The staff for the research division involved in this proposal includes a full time statistician. Mrs. Luo has a Master degree in Public Health. She has over 15 years of experience as a statistician. She has expertise in analyses using SAS and is capable of using R and STATA as well. Given the space is shared with additional VA research teams, this offers an environment for collaboration and trouble shooting with other statisticians when needed in close proximity.

***Washington University in St. Louis*:** Washington University in St. Louis continues as an active participating site in the ongoing research. A brief updated overview of resources is outlined below:

Clinical Facilities:
Barnes Jewish Hospital: Barnes Jewish Hospital is the largest hospital in Missouri. The medical staff consists of over 1,800 attending physicians. The hospital contains 1,315 licensed beds providing care to over 50,000 admissions annually.

Siteman Cancer Center: Siteman cancer center is the only National Cancer Institute designated Comprehensive Cancer Center in Missouri and within a 240-mile radius of St. Louis. Over 300 clinicians and researchers staff it. It is a member of the National Comprehensive Cancer Network. Given the distance to neighboring comprehensive centers, Siteman has a large referral basis with patients coming from all over the state to receive care.

Research Facilities: Washington University in St. Louis is a world-class, robust research environment with extensive academic and research resources and ideal opportunities for collaboration.

APPENDIX Posters and Submitted Publications (To Follow)

Cancer Treatment and Research Communications

A Real World Study of Pneumonitis in Non-Small Cell Lung Cancer Patients Receiving Durvalumab Following Concurrent Chemoradiation

--Manuscript Draft--

Manuscript Number:	CTC-D-22-00326
Article Type:	Original article
Keywords:	checkpoint inhibitors; Immunotherapy; adverse events; COPD Severity; Hypersensitivity Reaction
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	Kristen M. Sanfilippo, MD
	Jesse W. Keller, MD
Abstract:	Background: Locally advanced non-small cell lung cancer (LA-NSCLC) treated with the PD-L1 inhibitor durvalumab has been associated with significant rates of pneumonitis, which has led to higher rates of discontinuation of therapy in real world populations. Thus far there has been no consensus in the literature on the impact of pneumonitis on survival. Patients: Veterans receiving durvalumab between from 12/5/2017 - 4/15/2020 were identified using VA Informatics and Computing Infrastructure (VINCI) data services. Patients were followed through 9/14/2021. Methods: Development of clinical pneumonitis was assessed through review of documentation and graded using CTCAE 4.0 criteria. Univariate logistic regression analysis evaluated for associations between age, race, co-morbidity index, chemotherapy regimen, COPD severity, and development of clinical pneumonitis. Progression free survival (PFS) and overall survival (OS) were evaluated using Kaplan Meier methods. Results: 61 patients developed clinically significant pneumonitis, 7 patients developed grade 5 pneumonitis (death from pneumonitis). The median OS in patients that developed pneumonitis was 27.8 months versus 36.9 months in patients that did not develop pneumonitis (p=0.22). COPD severity, race, age at durvalumab start date, chemotherapy regimen, and Romano comorbidity index were not significant predictors of pneumonitis. Cox proportional hazards analysis failed to demonstrate an association between the development of pneumonitis and risk of death. Conclusion: The incidence of clinically significant pneumonitis is higher than noted in the PACIFIC trial in this cohort, however this high rate of pneumonitis does not have an impact on OS or PFS. There are no consistent clinical predictors of pneumonitis including COPD severity.
Suggested Reviewers:	Thierry Jahan, MD Professor of Medicine, University of California San Francisco thierry.jahan@ucsf.edu significant experience in thoracic malignancies including lung cancer

	Daniel Morgensztern, MD Professor, Washington University in St Louis danielmorgensztern@wustl.edu editor and co-editor of multiple journals focused on lung cancer
	Bruna Pellini, MD Moffitt Cancer Center bruna.pellini@moffitt.org specializes in lung cancer and other thoracic malignancies

Cover Letter

DEPARTMENT OF VETERANS AFFAIRS
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In reply refer to: 657/111C-JC

To the editor, September 20, 2022

This study looks retrospectively at patients with locally advanced non-small cell lung cancer treated with the PD-L1 inhibitor durvalumab at the Veterans health association in order to evaluate rates of pneumonitis, and the association between pneumonitis and survival. It also evaluates possible predictors of pneumonitis in this patient population. This study found that pneumonitis, particularly clinically significant pneumonitis (grade 2 or higher) occurs at a higher rate than predicted by the PACIFIC trial, the landmark trial that evaluated the efficacy of durvalumab. This shows that in a real-world cohort, clinicians should be vigilant to watch for the development of pneumonitis so treatment is not delayed as it may occur more often than previously expected. Additionally, this study found a higher rate (2%) of grade 5 (death from pneumonitis) pneumonitis than previously reported in the literature, meaning clinicians should carefully discuss the risk with individual patients while closely monitoring for this potentially deadly adverse event. However, this study found that development of pneumonitis does not affect overall survival or progression free survival. This is important as there has previously been no consensus on this association in the literature.

This study additionally found that 2% of patients developed a hypersensitivity reaction while receiving durvalumab. This has not been previously reported in the literature to our knowledge, and 2 of these cases required hospitalization. This means that hypersensitivity reactions are a potentially underrecognized consequence of durvalumab therapy, and clinicians should be aware of this possibility in order to not delay treatment.

Lastly this study found that there are no clinically significant predictors of pneumonitis including COPD severity which has not been previously evaluated as a predictor. This is important as it means even patients with severe COPD are potentially eligible for durvalumab therapy as it does not increase their risk for developing pneumonitis.

Sincerely,

Neha Akkad, MD

Highlights

- The risk of pneumonitis is higher in real world patients than in the PACIFIC trial
- There is a risk of a hypersensitivity reaction in patients receiving durvalumab
- There was no association between COPD severity and pneumonitis development

Title Page:

A Real World Study of Pneumonitis in Non-Small Cell Lung Cancer Patients Receiving Durvalumab Following Concurrent Chemoradiation

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Abstract

Background:
Locally advanced non-small cell lung cancer (LA-NSCLC) treated with the PD-L1 inhibitor durvalumab has been associated with significant rates of pneumonitis, which has led to higher rates of discontinuation of therapy in real world populations. Thus far there has been no consensus in the literature on the impact of pneumonitis on survival.

Patients:
Veterans receiving durvalumab between from 12/5/2017 - 4/15/2020 were identified using VA Informatics and Computing Infrastructure (VINCI) data services. Patients were followed through 9/14/2021.

Methods:
Development of clinical pneumonitis was assessed through review of documentation and graded using CTCAE 4.0 criteria. Univariate logistic regression analysis evaluated for associations between age, race, co-morbidity index, chemotherapy regimen, COPD severity, and development of clinical pneumonitis. Progression free survival (PFS) and overall survival (OS) were evaluated using Kaplan Meier methods.

Results:
61 patients developed clinically significant pneumonitis, 7 patients developed grade 5 pneumonitis (death from pneumonitis). The median OS in patients that developed pneumonitis was 27.8 months versus 36.9 months in patients that did not develop pneumonitis (p=0.22). COPD severity, race, age at durvalumab start date, chemotherapy regimen, and Romano comorbidity index were not significant predictors of pneumonitis. Cox proportional hazards analysis failed to demonstrate an association between the development of pneumonitis and risk of death.

Conclusion:
The incidence of clinically significant pneumonitis is higher than noted in the PACIFIC trial in this cohort, however this high rate of pneumonitis does not have an impact on OS or PFS. There are no consistent clinical predictors of pneumonitis including COPD severity.

Keywords: Checkpoint Inhibitors, Immunotherapy, Toxicities, COPD Severity, Hypersensitivity Reaction

Introduction:

Locally advanced non-small cell lung cancer (LA-NSCLC) comprises approximately one third of new NSCLC diagnoses. Unresectable disease is treated with definitive intent concurrent chemoradiation (CRT). Historically, patients were observed following completion of CRT. While effective, the 5-year overall survival (OS) with definitive CRT alone is approximately 25%. Durvalumab is a PD-L1 immune checkpoint inhibitor administered following completion of CRT. The landmark PACIFIC trial demonstrated a significant improvement in both progression free survival(PFS)[1] and overall survival(OS)[2]. As such, durvalumab following completion of CRT has become standard of care. The estimated OS and PFS have since remained promising and are estimated at 49.6% and 36.3% respectively at four years[3].

Immune checkpoint inhibitors are associated with a variety of complications. In patients receiving durvalumab for NSCLC, pneumonitis has been shown to be one of the most common[4]. This inflammatory condition of the lungs is a potentially fatal adverse effect of immunotherapy or radiation therapy, therefore the risk of pneumonitis is a key concern for patients receiving immunotherapy following CRT. The incidence of clinically important, grade 3/4 pneumonitis in the landmark PACIFIC trial was 3.4% (compared to 2.6% with placebo), and the rate of any grade pneumonitis was 19%[2]. In clinical practice, the observed rate of clinically significant pneumonitis is higher[5]. Smaller real world cohorts have reported the rate of any grade pneumonitis as anywhere from 19-35%[6,7,8]. The reported incidence of clinically significant grade 3 or higher pneumonitis has been reported from 6% to 15% in smaller real world cohorts and larger meta-analyses[9, 7, 10]. A study done on real world patients showed that this patient population had a higher rate of durvalumab discontinuation due to toxicity than the PACIFIC trial patient population[5]. Death from pneumonitis (Grade 5 toxicity) while rare (reported incidence around 1%) represents a serious consequence of therapy[11]. Altogether these studies suggest that pneumonitis is more common in real world settings than reported in clinical trials. Our study sought to explore the frequency of pneumonitis, the impact of pneumonitis on survival, and explore clinical predictors of pneumonitis in a real world cohort of US Veterans.

Several previous studies have evaluated multiple clinical and laboratory predictors of pneumonitis. The following characteristics including chemotherapy choice[6], lung volume receiving >20Gy(V20), sex, age, smoking status, presence of baseline pneumonitis, type of radiation, location of lesion[12] , PDL-1 expression[13], dose of durvalumab, ECOG, histology, time between radiation and durvalumab, relevant co-morbidities,[14] and Brinkman index[15] have not been found to be predictive of pneumonitis. There has been some incongruity in the literature however as some studies have found that V20, V40, V5, mean lung dose, and history of pneumonitis prior to durvalumab administration[16] are risk factors for grade 2 or greater pneumonitis, while others have found the opposite [17,11,18,19]. Taken together, reliable clinical and laboratory markers predictive of pneumonitis development have not been consistently reported.

The clinical impact of pneumonitis on patients receiving durvalumab is that they have higher rates of discontinuation of therapy[5,20]. Both discontinuation of therapy and development of pneumonitis may impact survival. One real world study showed that patients that experienced any grade pneumonitis had a lower 12-month OS, while others have shown that grade 2 or higher pneumonitis does not appear to be associated with worse OS or PFS[10, 20]. Given the high incidence of pneumonitis in this patient population and unclear impact on survival, this study

evaluates the incidence of pneumonitis and survival in a large nationwide real-world cohort of United States Veterans. This will become increasingly important in order to help make decisions about continuing versus stopping durvalumab therapy in patients with pneumonitis.

Patients:
Veterans receiving durvalumab between from 12/5/2017 through 4/15/2020 were identified using VA Informatics and Computing Infrastructure (VINCI) data services. Only patients with NSCLC who received chemoradiation and at least once dose of durvalumab were included. Individual patient records were reviewed using the Compensation and Pension Records Interchange software system/Joint Legacy Viewer. Patients were followed through 9/14/2021. This study was approved by the Washington University in St. Louis School of Medicine and Veterans Affairs St. Louis Healthcare System Institutional Review Boards prior to cohort assembly.

Methods:
This is a multi-center, population-based, retrospective cohort study evaluating patients with NSCLC treated with durvalumab following completion of concurrent CRT. Oncologic treatment history including chemotherapy received, dates and doses of durvalumab administration, radiation treatment history, date of progression, pulmonary function tests, PD-L1 percentage, and date of death were recorded through manual chart review (NA, TT).

The primary outcome of interest was development of clinical pneumonitis. This was assessed through review of documentation from oncology and pulmonology providers. Imaging reports were reviewed to assess for the presence of infiltrates. Pneumonitis grade was obtained directly from the medical record when available. If missing, clinical documents in combination of prescription of corticosteroids and supplemental oxygen administration were interpreted and graded using CTCAE 4.0 criteria. Patients with new radiographic infiltrates without documented clinical pneumonitis are considered asymptomatic, potential pneumonitis patients. Receipt of corticosteroids was confirmed through pharmacy records. COPD severity was graded based on the American Thoracic Society categories from 2005. The Romano adaptation of the Charlson comorbidity index was calculated using ICD-9 codes to develop a composite comorbidity score[21].

Univariate logistic regression analysis evaluated for associations between age, race, Romano co-morbidity score, chemotherapy regimen, COPD severity (determined by recorded FEV1), and development of clinical pneumonitis. Cox proportional hazards analysis was used to estimate hazard ratios for risk of death up to 1 and 2 years from durvalumab start date and controlling for potentially confounding variables (age, clinical stage and pneumonitis). PFS and OS (stratified by clinical pneumonitis) were evaluated using Kaplan Meier methods. Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

Results:
There were 284 patients with NSCLC at the VHA who received CRT followed by durvalumab between 12/5/2017 and 4/15/2020. Of these patients 1 was stage I, 21 were stage II, 228 were stage 3, the rest were unknown. (Table 1). The majority of patients had either adenocarcinoma (125) or squamous cell carcinoma (132). The median age at diagnosis was 68 for all patients included. Of the patients that PDL-1 expression was checked and recorded (112), 39 had <1%

PDL-1 expression, 41 had between 11% and 49% expression, and 32 had greater than 50% expression. Regarding co-morbidities, of this patient population 33% had type 2 diabetes, 10% had renal failure, and 18% had a prior autoimmune disease. Baseline FEV1 data was also collected on these patients. 51 patients had a normal FEV1, 33 had a mild impairment, 31 had a moderate impairment, 37 had a moderately severe impairment, 31 had a severe impairment and 17 had a very severe impairment, 80 were unknown. Chemotherapy regimen and radiation dose are summarized in the Table 1. Carboplatin and Paclitaxel was administered most commonly to 80% of patients. 59% of patients received > 54Gy of radiation. Durvalumab was completed in 101 (35%) of patients and was ongoing at time of review in 2 patients (1%). Durvalumab was discontinued due to disease progression in 84 patients (30%) and toxicity in 54 patients (21%).

Table 1 : Patient Demographics

Characteristics	All patients (n=284)
Stage	
I	1 (<1%)
II	21 (7%)
III	228 (80%)
Unknown	35 (12%)
Histology	
Adenocarcinoma	125
Squamous cell	132
Poorly differentiated	21
Mixed	1
Large cell	2
NOS	2
PDL-1 expression	
<1%	39 (14%)
11-49%	41(14%)
>50%	32 (11%)
Unknown	172 (61%)
PFTs	
No impairment	51 (18%)
Mild (FEV1 70-79%)	33 (11%)
Moderate (FEV 60-69%)	31 (11%)
Moderately severe (FEV 50-59%)	37 (13%)
Severe (FEV1 35-49%)	31 (11%)
Very severe (FEV1 <35%)	17 (6%)
Unknown	84 (30%)
Chemotherapy Regimen	
Carboplatin/Paclitaxel	226 (80%)
Platinum/pembrolizumab	25 (9%)
Platinum/etoposide	20 (7%)
Platinum/vinorelbine	1 (<1%)
Unknown or none	12 (4%)
Radiation dose	

<54Gy	9 (3%)
54-66Gy	140 (49%)
>66Gy	28 (10%)
Unknown	107 (38%)
Reason for Durvalumab Discontinuation	
Therapy completed	101 (35%)
Progression	84 (30%)
Toxicity	59 (21%)
Patient decision	23 (8%)
Death	11 (4%)
Therapy ongoing	2 (1%)
Unknown	4 (1%)

All reported toxicities are summarized in Table 2. 61 patients developed clinically significant pneumonitis, defined as grade 2 or higher. 106 patients developed imaging changes possibly consistent with pneumonitis, but of these only 9 were clinically defined as grade 1 pneumonitis in EMR (electronic medical record) notes. Of the total cohort 9% developed grade 2 pneumonitis, 9% developed grade 3 pneumonitis, 1% developed grade 4 pneumonitis, and 2% developed grade 5 pneumonitis. Most patients who developed pneumonitis did not resume it. 19 patients (27%) who developed clinically significant pneumonitis were re-challenged. Of these re-challenged patients, 15 patients (79%) tolerated durvalumab without redeveloping pneumonitis. 2 patients got pneumonitis a second time and therapy was stopped again. Other toxicities noted in this study were endocrinopathies (13), hepatitis (2), colitis (2), hypersensitivity reactions (5), and arthritis (1).

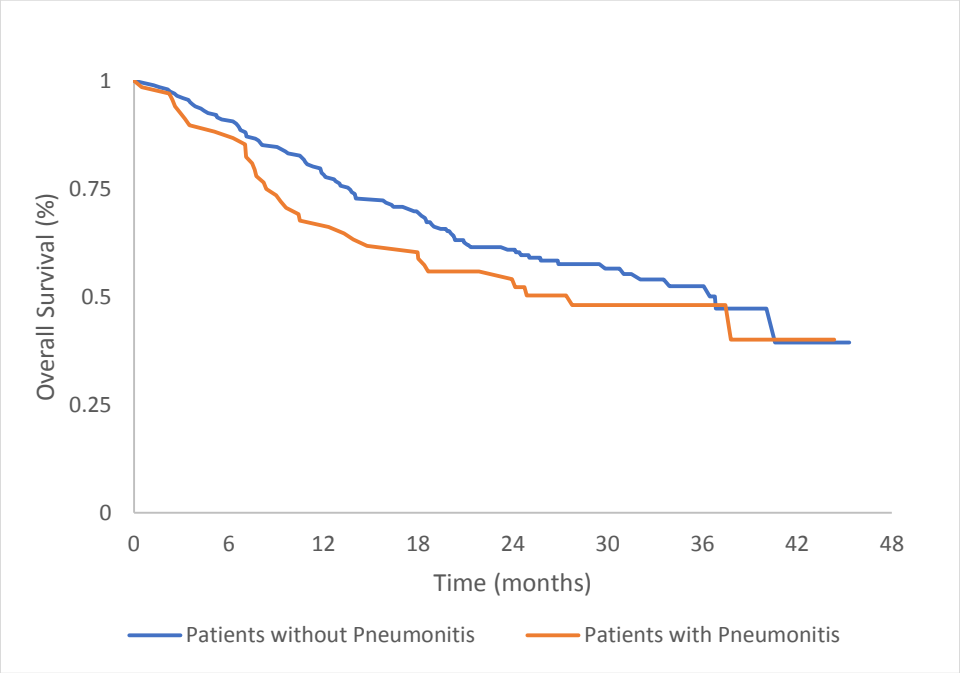
Table 2: Toxicities

Toxicity	All patients (n=284)
Pneumonitis	
Grade 2	25 (9%)
Grade 3	26 (9%)
Grade 4	3 (1%)
Grade 5	7 (2%)
Hepatitis	2 (<1%)
Endocrinopathy	13 (5%)
Colitis	2 (<1%)
Hypersensitivity reaction	5 (2%)
Arthralgia	1 (<1%)

The median overall survival (OS) in patients that developed pneumonitis compared to those who did not was 27.8 months and 36.9 (p=0.22), respectively. (Figure 1) Similarly progression free survival (PFS) was not significantly different in patients who developed pneumonitis versus those that did not (14.4 months vs 17.4 months (p=0.38)) (Figure 2). Our study additionally looked at clinical and laboratory predictors of pneumonitis and found that COPD severity, race,

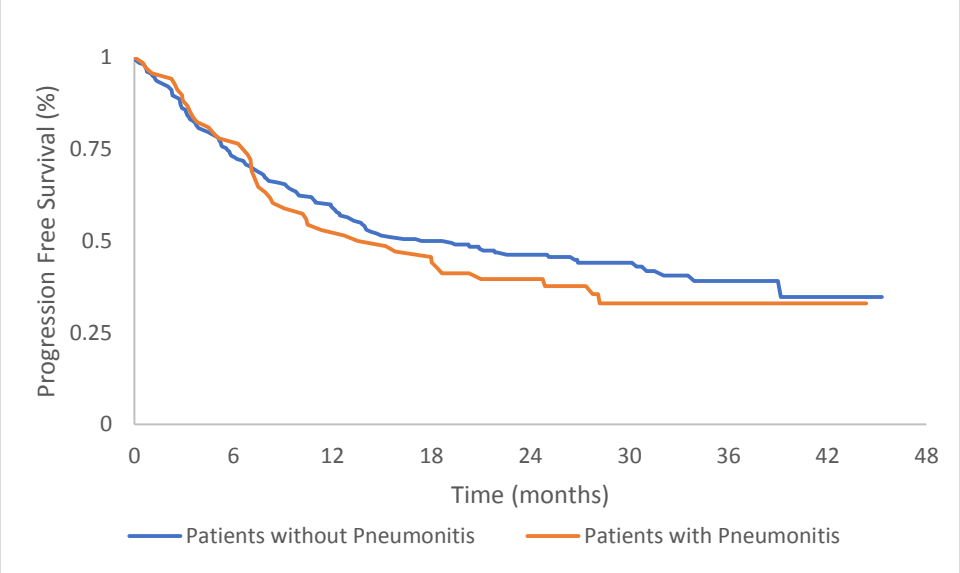
age at durvalumab start date, chemotherapy regimen, and Romano comorbidity score were not significant predictors of pneumonitis (Table 3). Cox proportional hazards analysis failed to demonstrate an association between the development of pneumonitis and risk of death.

Figure 1: Overall Survival



Kaplan Meir curve showing overall survival in patients receiving durvalumab for NSCLC that developed pneumonitis vs. those that did not up to 48 months

Figure 2. Progression Free Survival



Kaplan Meir curve showing progression free survival in patients receiving durvalumab for NSCLC that developed pneumonitis vs. those that did not up to 48 months

Table 3: Clinical Predictors of Pneumonitis

Characteristic	**Risk Factor**	**Odds Ratio**	**Confidence Interval**
Age	60-69 (v <60)	1.15	0.43 – 3.10
	>70 (v <60)	1.67	0.63 – 4.46
Co-morbidities	Romano Co-morbidity index	1.03	0.93 – 1.15
Race	Black (v white)	0.81	0.38 – 1.74
	Other (v white)	0.97	0.10 – 9.52
Chemotherapy	Platinum+pembrolizumab (v carbo/taxol)	2.43	1.02 – 5.82
	Platinum+etoposide (v carbo/taxol)	1.46	0.53 – 4.00
Time from Radiation to Durvalumab Initiation	<= 30 days vs. 31-45 days	1.26	0.56 – 2.87
	46-60 days vs. 31-45 days	1.94	0.85 – 4.39
	>=61 days vs. 31-45 days	1.46	0.67 – 3.18
COPD severity	Mild impairment (v. none)	2.29	0.87 – 6.00
	Moderate impairment (v. none)	0.66	0.21 – 2.11
	Moderate to severe impairment (v. none)	1.79	0.70 – 4.58
	Severe impairment (v. none)	0.86	0.28 – 2.63
	Very severe impairment (v. none)	0.97	0.27 – 3.56

Discussion:

In this multi-center, population-based cohort study of US Veterans with NSCLC treated with durvalumab, the incidence of clinically significant pneumonitis (defined as grade 2 or higher) was 21% which included 13% with grade 3 or higher pneumonitis. In the landmark PACIFIC trial, grade 3/4 pneumonitis occurred in 3.4% of patients[2]. Prior studies have similarly demonstrated a higher risk of pneumonitis then reported in clinical trials[9,7,10]. Interestingly, in our cohort, 7 patients had grade 5 pneumonitis and died from these complications. The PACIFIC trial did not report grade 5 pneumonitis[1]. Our study shows a higher rate of grade 5 pneumonitis than what has been reported in previous studies, with others reporting the rate of grade 5 pneumonitis around 1%[11]. However, our study shows that pneumonitis does not affect OS or PFS

across all patients. The current literature has not been consistent if pneumonitis has an effect on survival, our study is one the largest populations in which survival has been evaluated.

Together this study confirms higher rates of clinically significant pneumonitis in a multi-center real world population that other studies have shown. This study also suggests that the risk of potentially fatal pneumonitis is not minimal, and clinicians should carefully discuss this risk with individual patients while closely monitoring for this potentially deadly adverse event. Our study found there is no association between pneumonitis and risk of death up to 1 or 2 years when age, cancer stage and co-morbidities are taken into account. However, durvalumab was discontinued in most patients who developed pneumonitis. Whether there will be long term impacts on survival due to this discontinuation requires longer follow up. There was no difference in PFS suggesting that disease control was not impacted by the discontinuation of durvalumab.

Additionally our study reports 5 patients who had a hypersensitivity reaction (2%) while receiving durvalumab. The incidence of hypersensitivity reactions has not been previously reported in the literature in NSCLC patients receiving durvalumab to our knowledge. This is clinically significant as two reactions resulted in hospitalizations. Hypersensitivity reactions to durvalumab are potentially under recognized. This is an important aspect of treatment that clinicians should be aware of as it is treatable with prompt interventions during infusion.

Similar to other studies, our study showed there are no significant predictors of pneumonitis including COPD severity, race, age at durvalumab start date, chemotherapy regimen, and Romano comorbidity score. COPD severity has not been previously evaluated as a predictor of pneumonitis in this population, however it does not appear to be a risk factor meaning a severe impairment should not prohibit clinicians from administering durvalumab to these patients.

Conclusion:

In conclusion, this study confirms that rates of clinically significant pneumonitis are higher than noted in the PACIFIC trial in NSCLC patients receiving durvalumab. However as has been inconsistent in the literature, this high rate of pneumonitis does not have an impact on OS or PFS. Moreover, this study failed to demonstrate clinical predictors of pneumonitis including COPD severity.

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Author Contributions Statement

Neha Akkad: Conceptualization, Investigation, Writing **Theodore Thomas:** Conceptualization, Investigation, Writing **Suhong Luo:** Methodology, Software, Formal Analysis **Eric Knoche:** Conceptualization **Kristin Sanfilippo:** Conceptualization **Jesse Keller:** Conceptualization, Writing, Supervision, Funding acquisition

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Neha Akkad: no conflicts of interest

Theodore Thomas: no conflicts of interest

Suhong Luo: no conflicts of interest

Eric Knoche: no conflicts of interest

Kristen Sanfilippo:

2 month COI =
Expert Case Review for Quinn Johnston, not related to the published work
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Expert Case Review for Quinn Johnston, not related to the published work
Consultant for Health Services Advisory Group, not related to the published work
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Jesse Keller: no conflicts of interest

Infusion Time and Overall Survival in Melanoma Immunotherapy Recipients

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INTRODUCTION

- Circadian rhythms can impact lymphocyte trafficking, immune cell modulation, tumor microenvironment, and chemotherapy efficacy
- Recent research has shown improved overall survival among melanoma patients receiving immunotherapy infusions early versus late in the day
- We performed a similar analysis to assess the role of time-of-day infusion on immunotherapy outcomes among a large cohort of US Veterans treated with immune checkpoint inhibitors for melanoma

STUDY OBJECTIVES

- To determine the relationship between the time of day of infusion and overall survival and risk of death in veterans receiving immune checkpoint inhibitors for melanoma

METHODS

- All Veterans with melanoma receiving FDA-approved immune checkpoint inhibitor from 3/1/2011 to 4/1/2020 in the VA Informatics and Computing Infrastructure databases were included in the cohort, including PD-L1, PD-1 and CTLA4 agents
- ICD-9 and ICD-10 codes were utilized to identify a malignant diagnosis
- Survival outcomes were obtained from the VA Vital Status database
- Time of infusion was obtained via bar code medication administration records
- Patients were selected for comparison if they received > 50% of their infusions either before 1PM (early) or after 1PM (late)
- Survival analysis was conducted using the Kaplan-Meier method for overall survival at 2 years
- Cox proportional hazards analysis (CPH) was used to estimate multivariable hazard ratios (HRs) for Overall survival (OS) at 2 years with age, race, body mass index (BMI), and comorbidities as covariates
- Propensity score matching on age and comorbidities was performed 1:1

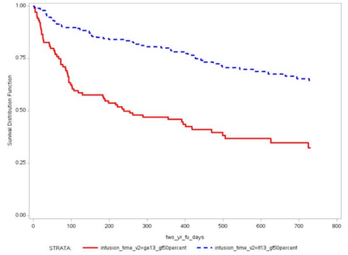
RESULTS

- A total of 399 Veterans received immune checkpoint inhibitor treatment for melanoma during the study period (One hundred eighty-eight patients received > 50% of their infusions early, 104 patients received > 50% late)
- There was no difference in baseline age, body mass index, or comorbidities between the late and early groups
- Two-year OS among late vs early groups showed worsened overall survival with late-day infusions (median 8.1 months vs not reached)

Table 1:
Baseline Characteristics of Early vs Late Infusion Patients

Demographic clinical characteristics	Total (N=292)		P-value
	early treatment	late treatment	
Age (mean years)	68.7	69	0.82†
Male (%)	98.9	93.3	0.007*
Charlson score index (mean)	3.3	3.8	0.15†
Race (%)			0.01*
White	97.9	91.4	
non-whtie	2.1	8.6	
BMI categroy (%)			0.16*
BMI<18.5	2.1	1.9	
18.5<=Bmi<25	23.4	35.6	
25<=Bmi<30	36.7	32.7	
BMI>=30	37.8	29.8	
* Chi-square test			
† T-test			

Figure 1: Kaplan Meier Analysis of Overall Survival At 2 Years by Time of Infusion (BLUE < 1PM vs RED > 1PM)



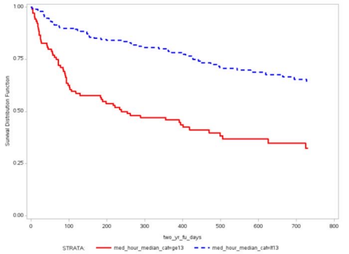
RESULTS (cont.)

- Cox proportional hazards analysis for overall survival at 2 years found that late infusions were associated with an increased risk of death (HR 2.89 [1.99-4.19])
- Propensity score matched cohorts (103 patients per arm) showed decreased overall survival associated with late vs early infusion (median overall survival 7.8 months vs not reached)
- CPH analysis of PSM cohorts showed an association between late infusion and increased risk of death at 2 years (HR 2.56 [1.67-3.94])
- Sensitivity analyses included assessment of survival by median and mean time of infusion < 1PM vs > 1PM showed persistence of overall survival benefits with early infusion

Table 2:
Cox Proportional Hazards Model for Propensity Score Matched Cohort (Early vs Late): OS at 2 Years

Parameter	Hazard Ratio	95% Confidence Interval
Late Infusion Time (50% after 1PM)	2.562	1.667 - 3.938
Age	1.004	0.984-1.025
Race (Caucasian)	0.708	0.320-1.567
BMI (< 18.5)	2.147	0.483-9.531
BMI (25 - 30)	0.684	0.419-1.116
BMI (30 - 35)	0.542	0.290-1.014
BMI (>35)	0.911	0.498-1.665
Romano Comorbidity Index	1.019	0.951-1.092

Figure 2: Kaplan Meier Analysis of OS At 2 Years by Median Time of Infusion (BLUE < 1PM vs RED > 1PM)



CONCLUSIONS

- Early day infusion time was associated with improved overall survival among melanoma immunotherapy recipients
- Findings remained significant in a propensity score matched multivariate statistical model
- The retrospective nature of this study leaves open the possibility of potential unmeasured bias leading to observed results

FUTURE WORK

- The findings of this study support future research focusing on infusion time-of-day and efficacy of immune checkpoint inhibitors
- We plan to evaluate distance from the infusion center as a potential confounding variable
- Potential randomized prospective studies could better answer this interesting clinical question

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Early Infusion Time is Associated with Improved Survival in Lung Cancer Immunotherapy Patients

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INTRODUCTION

- Prior literature has shown an association between early day immune checkpoint inhibitor infusion times and improved overall survival among Melanoma patients.[1]
- Components of the circadian clock can affect tumor oncogenesis due to disruption of cellular processes such as nutrient metabolism and protein folding.[2]
- Some studies have shown that timing medications based on the circadian rhythm could reduce adverse events[3]. Smaller studies have shown some decrease in chemotherapy toxicity and increased effectiveness with chronomodulated therapy[4].
- The circadian clock also affects the immune system[5]. There is a paucity of data on the impact of chronomodulation on immunotherapy in lung cancer, however.

STUDY OBJECTIVES

- Investigate the impact of early vs late immune checkpoint inhibitor infusion time in a VA cohort of patients with metastatic or unresectable lung cancer.

METHODS

- VA Informatics and Computing System was used to identify all ICI recipients and veterans receiving ICI (PD-L1, PD-1, CTLA4) from 3/1/2020 to 4/1/2020 were included in the cohort.
- Survival outcomes were obtained from the VA Vital Status database and Time of Infusion was obtained from Bar Code Medication Administration records.
- Patients were included in study if they received greater than 50% of infusions either before 1 PM (early cohort) or after 1 MP (late cohort).
- Kaplan-Meier Method was used to calculate Overall Survival at 2 years. Propensity matched KM analysis for age and comorbidity matched cohort was also done for OS at 2 years with.
- Cox proportional hazards analysis (CPH) was used to estimate multivariable hazard ratios (HRs) for OS at 2 years with age, race, body mass index (BMI), and comorbidities as covariates. Propensity matched CPH for age and comorbidities was also used to estimate hazard ratios.

RESULTS

Table 1: Baseline characteristics of early and late infusions

Demographic Clinical Characteristics	Total (N=1451) Early Treatment n=1004	Late Treatment n=447	P-value
Age (mean years)	68.8	68.7	0.94†
Male (%)	96.1	95.5	0.60*
Charlson score index (mean)	4.4	4.6	0.36†
Race (%)			0.12*
White	81.2	77.6	
non-whtie	18.8	22.4	
BMI categroy (%)			0.13*
BMI<18.5	4.7	7.4	
18.5<=Bmi<25	44.3	46.1	
25<=Bmi<30	31.2	27.7	
BMI>=30	19.8	18.8	

* Chi-square test

† T-test

Table 2: Propensity Matched Cox Hazard Model for early and late infusions

Parameter	Hazard Ratio	95% confidence limits
Late Infusion Time	1.546	1.312-1.821
Age	1.01	.999-1.021
Caucasian Race	1.157	.939-1.427
BMI<18.5	1.294	.944-1.776
BMI 25-29.9	0.782	.645-.949
BMI 30-35	0.629	.481-.823
BMI >35	0.627	.426-.923
Romano Index	1.043	1.015-1.071

RESULTS (cont.)

Figure 1: Non propensity matched Kaplan Meier Analysis for 2 year OS.

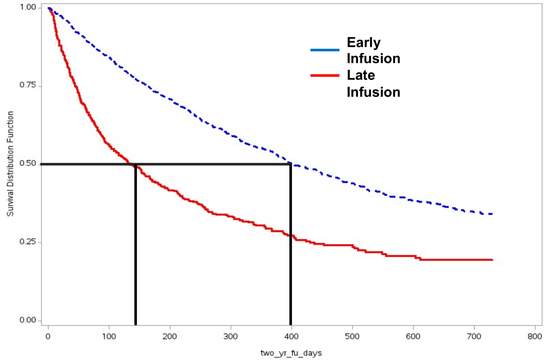
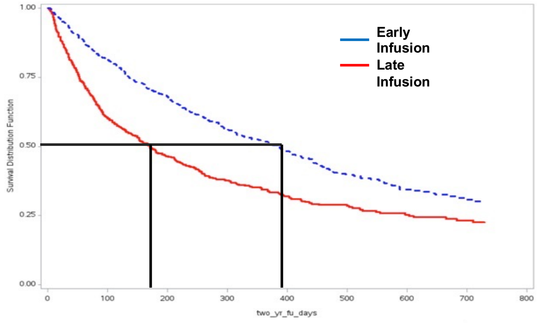


Figure 2: Propensity matched Kaplan Meier Analysis for 2 year OS when matched for age and comorbidities.



Results

- 1451 patients received >50% of infusions either before 1 PM (1004) or after 1 PM (447). Baseline demographic variables similar between groups.
- K-M analysis of 2 year OS showed improved OS with early day infusions (Median OS 14.2 vs 7.3 months). Propensity Matched Cohort KM analysis for age and comorbidities showed similar improved OS in early infusion (13.6 vs 6.6 months).
- Cox Proportional Hazards Model for OS at 2 years with age, race, BMI and comorbidities as covariates showed late infusions were associated with an increased risk of death (HR 1.622 [1.217-1.892]) compared to early infusions. Propensity Matched CPM for age and comorbidities showed late infusions were associated with increased risk of death (HR 1.54 [1.312-1.821]).

Conclusions

- Early day infusion time was associated with improved overall survival among lung cancer immunotherapy recipients. Findings similar with propensity matched cohorts as well.
- There is potential for bias given the retrospective nature of the study

FUTURE WORK

- Randomized prospective trials could help build on the preliminary data.
- Distance from infusion center could be a possible confounding variable, and plan to evaluate for this.

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